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Evaluating Retention in Medical Care and its Impact on the Health Outcomes of Individuals Living with Human Inmmunodeficiency Virus

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EVALUATING RETENTION IN MEDICAL CARE AND ITS IMPACT ON THE HEALTH OUTCOMES OF INDIVIDUALS LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
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By
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ABSTRACT OF DISSERTATION

EVALUATING RETENTION TO HIV MEDICAL CARE AND ITS IMPACT ON THE HEALTH OUTCOMES OF INDIVIDUALS LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

In the last few years, engagement in medical care among individuals living with HIV has become a major priority among HIV medical providers and public health researchers. Engagement in medical care is an important concept as it involves the process of linking newly diagnosed individuals into medical care and retaining those individuals in care throughout the course of their infection. Although there have been major advances in the management of HIV, like the advent of Highly Active Antiretroviral Therapy, morbidity and mortality due to HIV cannot be fully reduced if the individual does not optimally retain in care. Retention in HIV medical care has become an emerging topic in HIV research, but there still remains a scarce amount of research on how to properly define retention, understand its predictors, and how it impacts HIV outcomes.

The purpose of this dissertation was to evaluate retention in HIV medical care among individuals diagnosed with HIV and seeking care at an urban infectious disease clinic in Kentucky. The three specific aims of this dissertation were to: (1) compare methods in measuring retention in HIV medical care; (2) determine the predictors of poor retention in care and assess the effect of non-HIV related comorbidities have on retention over time; and (3) determine the impact early retention to medical care has on time to viral load suppression and rebound among individuals initiating Highly Active Antiretroviral Therapy.

A retrospective cohort study was conducted employing a medical chart review, and patients who sought HIV care at the Bluegrass Care Clinic between January 1st 2003 and May 1st 2011 were eligible for the study. There were 1,358 patients included in the study and these individuals were followed until December 31st, 2011.

The results suggested that individuals living with HIV should seek care at least once every six months (visit constancy) and that only 48.6% of the study population obtained optimal retention over time. Over time the rate of retention decreased among the study sample and those with optimal retention were more likely to suppress their viral loads compared to poor retainers.

KEYWORDS: HIV/AIDS, Retention in Care, Visit Constancy, Viral Load Suppression, Viral Load Rebound

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November 12th, 2012
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EVALUATING RETENTION TO HIV MEDICAL CARE AND ITS IMPACT ON THE HEALTH OUTCOMES OF INDIVIDUALS LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

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November 12th, 2012

This dissertation is dedicated to my partner TJ. Thanks for all of your encouragement, love, and support.

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CHAPTER ONE

Introduction

Due to advances in the clinical management of individuals infected with Human Immunodeficiency Virus (HIV), most notably the advent of Highly Active Antiretroviral Therapy (HAART), the HIV medical community has witnessed dramatic reductions in morbidity and mortality from HIV infection.[1-4] HAART has been shown to improve $CD4^+$ cell counts as well as improve the chance of sustaining HIV RNA plasma viral loads (VL) below 50 copies per milliliter.[2,3,5] The use of HAART has also been shown to reduce the rate of hospitalizations, opportunistic infections, Acquired Immune Deficiency Syndrome (AIDS), and death.[2-8] One study conducted by Walensky et al, estimated that at least 3 million years of life have been saved in the United States (U.S.) since the introduction of HAART.[2] However, clinical management of HIV can only be successful if individuals infected with HIV are identified and linked to medical care early, and retained in medical care.[9] It is estimated that over a million individuals in the U.S. are living with HIV, and roughly 21% of them are unaware of their infection [10-12] and approximately 31% of newly diagnosed individuals delay linkage to HIV medical care for 6 months or longer. [13]

Even with the early identification of HIV infection and initial linkage to care, optimal retention in HIV medical care is desirable to ensure full access to treatment benefits. It is extremely important for individuals living with HIV to have consistent contact with their HIV medical provider, regardless of whether or not the individual has initiated HAART. An individual, who has not yet initiated HAART, needs consistent contact with their HIV medical provider so disease progression can be monitored and HAART can be initiated when appropriate. Individuals, who have already initiated HAART, need consistent contact with their medical providers to monitor the effects of HAART, assess for complications, and ensure the risk of drug resistance is reduced.[9,14,15]

Linkage to care and retaining individuals living with HIV in medical care have become a persistent challenge among HIV medical providers and has become a major priority for both medical providers as well as public health organizations.[13,14] The Centers for Disease Control and Prevention (CDC) estimate that roughly one-third of diagnosed individuals are not receiving care (linkage)[11] and it has been estimated that approximately 25 – 30% of individuals who initiate outpatient HIV medical care, do not retain in care after one year.[12,16,17]

Retention in care is a major problem for HIV care providers because it does not allow individuals living with HIV to be properly monitored during the course of their infection.[14,15,18-20] Individuals who fail to retain in care miss their opportunity for timely initiation of HAART, treatment adherence support, and monitoring of $CD4^+$ cell counts and VL response.[14,15,19,21,22] The Department of Health and Human Services (DHHS) recommends individuals newly diagnosed and linked into care have their CD4+ cell counts and VLs observed every 3 to 4 months until their clinical response is stable.[23] Studies have shown that individuals who have poor retention in care have a higher risk of VL and CD4+ cell count failure[21,24-26], and risk acquiring AIDS defining illnesses (ADIs)[27], and death[21,27-29] compared to those individuals who have optimal retention in care. One study conducted by Giordano et al., estimated that individuals with poor retention compared to those with good retention (at least one clinic visit every 6 months) were almost 2 times more likely to die.[28] From a public health perspective, it is important to retain individuals in HIV medical care, as this may alleviate complications related to AIDS and promote behavior changes which could possibly reduce the risk of HIV transmission.[14-16,21,30,31]

Over the past few years, retention in HIV medical care has been given significant attention from the HIV research and clinical community, and has been recognized as a vital part in optimizing individuals' outcomes.[13-15] Although there is an emergence of interest in

this topic, there still remains a scarcity of research. Continuous engagement in HIV care without any interruption of access to HAART and other treatment is the main premise of retention.[14,21,32] One major challenge for clinicians and researchers who are interested in studying retention in care is deciding on how to best measure retention. Like adherence to medication studies, retention in care has multiple measurement techniques that can be used for determining retention in care.[13-15] The challenge is deciding which retention measure to use and which measure most accurately predicts HIV clinical outcomes like VL suppression, $CD4^+$ cell count failure, and AIDS progression.

Measuring retention in care can be difficult in some research and clinical settings due to the dynamic nature of HIV clinical cohorts. According to a small number of researchers in this field, there are approximately five retentions in HIV clinical care measures (gaps in care, missed visits, visit adherence, visit constancy, and the Health Resources and Services Administration HIV/AIDS Bureau (HRSA) performance measurements). There is no clear preferred standard.[13-15] It is important for researchers, in this field, to have a lucid idea of which retention measure is appropriate for their cohort, as well as which measure will more accurately predict specific clinical outcomes.

Although most studies have established predictors of poor retention in care and how poor retention may affect certain clinical outcomes, these studies have focused on only one retention measure and employed a short follow-up period (≤3 years).[9,22,27,33,34] To our knowledge, no study has attempted to compare multiple retentions in care measures and determine which measure most accurately predicts clinical outcomes like VL suppression and $CD4^+$ cell count failure. The purpose of this dissertation is to evaluate retention in HIV medical care, observe how retention changes over time, and understand the association between poor retention and poor HIV clinical outcomes. The three specific aims of this dissertation are to:

1. Compare three different retentions in care measures and evaluate the association between optimal to poor retention and immunological and virological outcomes.
2. Determine the predictors of poor retention and assess the effect non-HIV related comorbidities have on retention over time.
3. Employ parametric time to event methods to determine the effect poor retention has on time to viral suppression and viral rebound, among patients who have initiated HAART.

It is hypothesized that those individuals who do not retain in care consistently throughout the course of their infection will be more likely to have a $CD4^+$ cell count failure, less likely to have a viral suppression, and more likely to have a viral rebound compared to those individuals who do retain in care. The remaining sections of this dissertation will be divided into five chapters. The chapters in this dissertation will help guide clinicians and public health researchers in defining retention in care, identifying predictors of poor retention, and developing ways to improve viral suppression.

The purpose of chapter two, "Measuring Retention in HIV Medical Care: A Literature Review," was to assess the different methods used by clinicians and researchers to define retention in medical care among individuals living with HIV. The chapter described five different retention measurement techniques: visit constancy, missed visits, visit adherence, gaps in care, and the HRSA performance measure. The chapter focused on defining each retention measure, describing the advantages and disadvantages of employing each measure, and presenting data from studies that observed these measures. There is no standard method in defining retention in care, but the predictors for poor retention appear to be similar across studies and it appears to impact clinical outcomes.

In chapter three, "A Comparison Study of Methods for Measuring Retention in HIV Medical Care," results of a study to compare methods used for measuring retention in medical care are presented. Three methods in measuring retention in care (visit constancy, gaps in care, and the HRSA performance measure) were evaluated and compared to one another. Using receiver operating characteristic curves, retention measures were compared based on their ability to predict individuals with a suppressed VL and CD4+cell count failure. To our knowledge, this is one of the first studies to compare retention measures' ability to determine viral suppression and CD4+ cell count failure. A medical chart review was conducted and 1,358 patients were abstracted from the records and included in the analysis. The results from this chapter can be used to guide clinicians in choosing the appropriate retention measure.

The fourth chapter, titled "Impact of non-HIV Related Comorbidities on Retention in HIV Medical Care: Does Retention Improve over Time," presents results on a study that was conducted to identify predictors of retention in care as well as determining how factors like non-HIV related comorbidities and ADIs impact retention over time. Researchers studying retention have generally restricted their study time periods to 1 to 3 years. There is a lack of research on how retention in care affects the population over time. In particular how factors like non-HIV related comorbidities impact retention over time. Using visit constancy as the retention measure, the patient population included in this retrospective cohort study was followed for a mean of 5.75 years. A multinomial regression was used to determine predictors of the retention groups and generalized linear mixed models were used to determine whether retention in care improved over time.

The fifth chapter, titled "Impact of Retention in HIV Medical Care on Time to Viral Load Suppression and Rebound among Individuals Initiating HAART," presents the results on the study conducted to determine how retention in care impacts time to viral

suppression and time to viral rebound. Initiating HAART has been shown to improve the chances of viral suppression, but little research has been conducted to assess the impact retention has on viral suppression once an individual has initiated HAART. Also, once an individual has achieved viral suppression, it is unknown how retention in care impacts the risk of viral rebound. Using parametric survival methods, the association between retention in care and time to viral suppression/rebound was assessed.

The sixth chapter concludes the dissertation. The chapter summarizes the findings presented in the previous chapters and discusses the implications on the individual as well as the public health prevention efforts. Recommendations for future research is presented in this chapter as there is still research to be done on retention in HIV medical care and strategies need to be developed and set in place to re-engage those individuals who have been lost to follow-up.

CHAPTER TWO

Measuring Retention in HIV Medical Care

A Literature Review

Background

Since the initiation of HAART into the clinical management of HIV, it has now been considered a manageable chronic disease by reducing the morbidity and mortality related to HIV.[5-7] Clinical and public health researchers have all demonstrated the significant benefit obtained by initiating HAART, but individuals can only obtain these benefits if they maintain consistent contact with their medical provider.[35,36] Engaging and retaining individuals living with HIV into medical care is extremely important and has become a major problem as patient dropout is common.[17,18,21] It is pertinent to diagnose individuals with HIV and link them into care early as well as engage them in regular and consistent care with their medical provider to maintain optimal health.[19,21] This test and treat approach has become an important step in making sure that individuals with HIV are managing their disease properly.[12]

Consistent contact with an HIV medical provider ensures that the individual will initiate the appropriate therapy on time and will be monitored regularly to maintain suppressed viral loads and reduce the risk of progression to AIDS.[13] It has been estimated that approximately 40% of patients do not retain in medical care, and this is a significant public health issue as it has been shown that optimal retention in care can suppress the replication of HIV, thereby reducing the risk of transmission of HIV to others.[13,31]

In order to achieve optimal health outcomes in persons infected with HIV, optimal retention must be maintained throughout the course of infection. HIV requires a lifelong commitment and treatment regimen, and it is important for clinicians to retain their patients in medical care and alleviate patient fatigue. The Department of Health and Human Services (DHHS) guidelines states that individuals initiating HAART should receive care every three months until VL has been suppressed and then every four to six months after suppression of the VL.[23] These recommended guidelines allow the individual to have their VL and $CD4^+$ cell counts to be monitored and appropriate treatment administered whether it is HAART or opportunistic infection prophylaxis.[23]

Similar to medication adherence studies, determining the methods needed to define retention can be difficult and may rely on the data and resources the clinic or research group has available.[13-15] There are multiple methods used in measuring retention, but there is currently no preferred method.[15] Researchers in this field of study have published many approaches in defining retention in care and have determined the predictors for each retention measure. It is essential to provide a clear framework for how retention is defined and measured is something that is essential to retention in care research.[14]

The purpose of this chapter is to provide an extensive review of the multiple approaches commonly used to study retention in care among individuals living with HIV. The goals of this review are to: 1. Define all retention in care measurements; 2. Describe the advantages and disadvantages of each measure; 3. Describe the established predictors of retention in care; and 4. Discuss the effects poor retention has on HIV clinical outcomes. The review concludes with a discussion of where we are now in this area of research and what this dissertation will add to the current literature.

Methods

Electronic databases (Pubmed, CINAHL, Embase, and Medline) were searched for appropriate literature published between 1997 and 2011. This time period was chosen because it ensured that the individuals in these studies had the opportunity to initiate HAART. The search included the following combined keywords: 1. HIV/AIDS; 2. Retention; 3. Missed clinic visits; 4. Gaps in care; 5. Utilization of Care; 6. Suppression and Rebound; 7. Adherence; 8. Survival; and 9. Comorbidities. Secondary searches were conducted by checking the reference lists of the articles obtained from the primary search. Selected articles were restricted to the following time frame: 1997 and 2011, and only articles published in English were accepted.

Retention in Care Measurements

Retention in care studies have been an emerging topic in HIV care research and researchers have published multiple studies describing retention in care, the predictors of poor retention, and the effects poor retention has on clinical outcomes.[14-16,21,22,24,27,33,37-43] Unfortunately, because there is no preferred method for defining poor retention in care, researchers have used multiple definitions for measurements of retention, allowing comparison of studies to be difficult.[15] Due to the growing interest in this research topic, a few reports have been published summarizing several of the retention measurements.[13-15]

The selection of a retention measure may be based on a number of factors which may include the purpose for measuring retention in care, the type of clinic visit data that are available, clinic scheduling practices, and computational issues.[15] Retention in HIV medical care can be measured and conceptualized in at least five different ways:

1. Missed clinic visits
2. Clinic visit adherence
3. Gaps in Care
4. Visit Constancy
5. HRSA performance measure

There is currently no 'gold' standard for measuring retention, and no research study to suggest which measure may be the best and most appropriate measure at defining retention.

Missed Clinic Visits/ Clinic Visit Adherence

A straight forward retention in care measurement that is widely used by clinical and public health researchers is missed clinic visits.[14,15] Regardless of the number of scheduled visits, this measure captures the number of missed visits during a specified time period and they are typically defined as the number of clinic visits missed ('no show') and do not include canceled or rescheduled visits in the retention measurement.[14,15] Multiple studies have used missed clinic visits as a measure of retention and are generally applied as either a dichotomous variable (yes/no)[29,33,34,44,45] or a count (number of missed visits).[27,46,47]

Clinic visit adherence is a retention measurement that is derived from missed clinic visits and it involves the use of visits scheduled as well as visits missed or attended.[15] Visit adherence can be defined as visit adherence or visit non-adherence.[15] Visit adherence is a proportion that captures the number of completed visits in the numerator and the number of all scheduled visits in the denominator and is normally presented as percentage.[15,35,46,48-50] Visit non-adherence is similar to visit adherence, but instead of the number of completed visits in the numerator, the number of missed visits is used.[15,35,45,46]

Mugavero et al. conducted a study in 2009 assessing missed visits and mortality in patients establishing initial outpatient HIV treatment.[29] The authors conducted a retrospective study nested within a prospective HIV clinical cohort study which evaluated patients establishing initial outpatient treatment at the University of Alabama at Birmingham 1917 HIV/AIDS clinic between January 1st, 2000 and December 31st, 2005. Participants in the study were followed for one year after initial care visit and a missed visit was defined as a primary HIV care visit where the participant did not call the clinic to cancel or reschedule. 'No Show' visits, as Mugavero called them, were recorded as a dichotomous measure with participants dichotomized as no missed visits or ≥ 1 missed visit. Of the 543 patients included in the study, approximately 60% of the cohort had at least one missed medical visit during the year of follow-up[29].

Numerous researchers have employed missed clinic visits as their retention in care measurement, because of its simplicity.[27,29,33-35,44-50] Missed clinic visits are easy to measure as it only involves the number of scheduled visits missed and does not involve timing between scheduled visits like the other measurements. Clinic visit adherence may be appropriate for research studies involving longer observation periods as this may allow for assessment of exposure/response relationships between retention and clinical outcomes.[14,15] Also, missed clinic visit studies allow for clinicians to monitor individual patient behaviors.[15]

A disadvantage in using missed visits as a retention measure is that missed clinic visits do not take into account individuals who are lost to follow-up, as individuals who are lost to follow-up and poorly retained in HIV medical care during a study period may be misclassified as clinic visit adherers' even though they do not have any scheduled visits to miss.[15] Clinics that use automatic rescheduling may over estimate the number of missed

visits and visit non-adherence as the patient contact information may not be updated and patients may not be aware of rescheduled visits. How to analyze cancelled clinic visits has become an issue for researchers in computing missed visits and visit adherence, as most researchers have removed missed visits due to cancellations from their calculation.[14,27,29,44,50] The timing between the cancelled visit and rescheduled visit should be taken into consideration when calculating missed visit or visit adherence, so the issue of misclassification can be handled.

Gaps in Care

Gap in care or loss to follow up is one other retention in care measurement that is relatively straightforward in measuring. This measurement involves only the clinic visits that were completed and the date for each clinic visit completed.[15] The gap in care measure calculates a time interval between two consecutive visits, and is defined in 4, 6, or 12 month intervals and whether the individual exceeds that specified interval.[15,17,38,40,43] Some studies have used 'loss to follow up' as a surrogate for gap in care, which is where the individuals who are seeking clinical care, drop out or have gaps greater than 12 or more months.[38,43]

A retrospective medical record analysis was performed in Harris County, Texas to measure the success with which patients newly entering outpatient care establish care. Scheduled and unscheduled clinic visits subsequent to the initial intake visit were abstracted from all medical records. The authors used gaps in care to describe the pattern of established care among those individuals living with HIV. The interval range between two visits was set at ≥6 months, and the patients who had a gap of 6 or more months between visits were defined as 'poorly established' in care. The authors also classified individuals who did not have any completed clinic visits after the initial intake as 'not established' (lost to follow-up) and those with multiple visits with gaps <6 months were classified as

'established' in care. Of the 404 patients included in the study, 48% had poor to no established care (11% were 'not established' and 37% were 'poorly established). The authors were able to show that almost half of the study population was either poorly retained in care or completely lost to follow-up, meaning that their risk of severe illness had increased.[51]

Similar to missed clinic visits, gaps in care is simple to compute, as you only need the dates of the completed visits and a difference between those dates (typically described in months).[15] This retention in care measure involves only completed visits, so a researcher does not need to be concerned with obtaining the number of missed clinic visits or the issues with automatic rescheduling. The gap in care measure is a great measurement for monitoring individual patient behavior and can be used for administrative tracking of patients.[15]

Although gaps in care are a fairly simple retention in care measure, it is not amenable for use as a time-varying covariate, so it may not be appropriate to use for longer observational studies. This could be due to the fact that you are dealing with individuals who may drop out and not return for lengthy periods of time, making it difficult to determine change in visit adherence over time. Gaps in care are a fairly crude measure, typically described as a dichotomous measure, and the appropriate length of a gap varies among studies.[15] A potential bias that may occur in employing only the gap in care retention measure is misclassification. If an individual completes at least two visits and the interval is within the specified gap (e.g. 6 or 12 months), they would be considered to have optimal care even though they may not have any more scheduled visits and become lost to follow up. This is an issue that researchers should consider when deciding to use gaps in care as the preferred retention in care measure.

Visit Constancy

Aside from missed clinic visits, visit constancy has become a widely used measurement in HIV retention studies.[13,15,21,22,28,36,42,43,52-57] Visit constancy is a retention measurement that observes the proportion of time intervals with at least one completed clinic visit.[15] Because treatment guidelines recommend that individuals complete laboratory assessments and clinic visits every 3 to 6 months, time intervals in the visit constancy studies have typically ranged between 3 and 6 months.[23] Most studies observe visit constancy as at least one clinic visit every 6 months for a specified time period (e.g. 1 year, 2 years, etc.).[21,22,52,53,57]

In 2011, Tripathi et al. conducted a retrospective study to determine rates of retention after initial linkage to care was established, in a cohort of newly diagnosed HIV – infected persons in South Carolina and to characterize factors associated with lower retention after initial entry into HIV care. The individuals included in the study were followed for two years, observed in 6 month intervals (total of 4 intervals), and categorized into four types of retainers in HIV medical care: 1) Optimal Care – at least one visit in four out of the four 6-month intervals; 2) Suboptimal Care - at least one visit in three out of four 6-month intervals; 3) Sporadic Care – at least one visit in two out of four 6-month intervals; and 4) dropout – no visits recorded over the 2 year interval. Of the 2,247 newly diagnosed individuals who initiated care during the observation period, 50% had optimal retention and 22% and 10% were sporadic retainers and dropouts, respectively. Tripathi was the first to categorize patients based on the number of 6 month intervals with a completed clinic visit.[21]

Visit constancy has become a widely used retention measure because it captures the number of visits an individual has completed within a specified time interval and it can be easily employed for use as a time-varying measure analytically.[15] Visit constancy is a great measure for longer observational periods as researchers can attempt to assess an exposure/response relationship between poor retention and clinical outcomes, and can provide medical providers with treatment recommendations and suggestions on interventions.[15] An advantage of visit constancy is that the measurement only requires completed clinic visits and does not require the use of missed clinic visits in the calculation, which could be difficult to obtain for settings that do not capture that information. Compared to gap in care, missed visits, and visit adherence, visit constancy is better equipped to account for lost to follow-up as these individuals will be considered dropouts.[15,21]

Compared to the other retention measures, visit constancy is more computationally challenging and determining the appropriate intervals may pose difficulties as this may differ based on the patient's disease severity. Determining whether the time interval (e.g. 3-6 months) is based on calendar time (every individual has the same interval dates) or each individual's unique interval date, which may be based on factors like the initial start date into care or initial start date of HAART, may pose more computational and programmatic difficulty.[14,15]

HRSA performance measure

The HRSA performance measure is a relatively new retention in care measurement, and it observes whether an individual completed 2 or more clinic visits with each visit separated by 3 or more months in time during a 12-month study period.[15,39,58] The performance measure is considered a hybrid measure as it incorporates elements of visit

constancy and gaps in care.[15] The HRSA performance measure is typically used by clinic administrators to determine performance relative to the clinic standards that have been recommended by the DHHS.[15,23,58]

Researchers have discussed the use of this measure as more of a performance measure (i.e. how well the specified clinic is keeping patients engaged in care) to help guide clinicians in developing interventions to increase retention. The measure can be used for clinic level quality assurance as well as administrative tracking and reporting.[15] An advantage of this hybrid measure is that it does not involve the use of missed clinic visits and only needs to capture completed visits to calculate the measure. The HRSA performance measure also overcomes the limitation of appropriate interval length observed with the other measures like visit constancy.[15,38,39,43] The performance measure is relatively straightforward, but is computationally complex, as it involves the timing of clinic visits. Researchers conducting studies in the retention in care area may not prefer to use the HRSA performance measure as it is not suitable for use as a time-varying measure.[15]

The HRSA performance measure has been endorsed by HRSA as well as the National HIV/AIDS Strategy (NHAS).[58,59] A goal set by NHAS is to increase the proportion of people living with HIV who are retained in care from 73% to 80%.[59] There have only been a few studies to include the HRSA performance measure as the retention in care measurement.[38,39,43] In 2012, Hall et al observed retention in care among 13 U.S. areas using the HRSA performance measure, and approximately 45% of the people living with HIV in the 13 U.S. areas had at least two visits separated by three or more months.[39]

Predictors of Retention in Care

Although there are multiple ways in defining retention in care, the common goal among clinicians and researchers is to comprehend factors that play a role in poor retention and to promote methods to prevent poor retention from occurring. In 2010, Marks et al. conducted a meta-analysis to determine the overall percentage of individuals living with HIV who are poor retainers in medical care. The authors demonstrated that regardless of the length in time measured and the type of retention measurement used in these studies; approximately 40% of individuals were poor retainers in care.[13] A national study conducted by Cohen et al, suggested that 49% of individuals linked into care were poor retainers in medical care.[11] This is a disconcerting statistic and it has become an important priority to identify which patients are at greatest risk for not being retained in medical care.

In the retention in care literature, demographic and behavioral characteristics found to be associated with poor retention include black and Hispanic race/ethnicity[21,28,29,33,35,40,46,50,52,56], younger age[21,29,33,35,37,40,54], female gender[36,54], heterosexual contact[46], less education[60], lack of health insurance or public health insurance (Medicaid)[29,40,52,55], history of or current illicit drug use[17,49,50,52,54,61], shorter duration of follow-up[17], lower income [60], and unemployment.[52,60] Clinical characteristics associated with poor retention have included mental health illness[14,62], the year of their HIV diagnosis, higher $CD4^+$ cell counts[17,28,55], absence of AIDS diagnosis at baseline[17,35,40], and AIDS defining illnesses (ADI) at baseline[35,50]. These studies of clinical characteristics may seem contradictory, but intuitively, they reflect expected health care seeking behaviors.[14] Patients who enter into care without any health problems initially may not make their appointments because they do not feel sick and feel that there is no need to seek care, but patients who are sick may not attend appointments because they feel too sick to attend an appointment.[14,50]

Other characteristics that affect retention in care have been lack of social support[35], stigma related to HIV status[63], distrust of the health system[64], hospitalizations[65], and use of ancillary services.[53,55] Patients may not attend their scheduled clinic visits because of conflicts with work, lack of transportation, family illnesses, and hospitalizations.[14,65] In 1999, Palacio et al. published a study involving HIV-infected women, and found that the 3 most common reasons for missing appointments were forgetfulness, conflict with multiple appointments, or feeling too sick to attend.[66] A study of newly diagnosed persons living with HIV/AIDS found that the negative stigma related to HIV was a major reason for patients not retaining in care or even initiating care.[63]

Finally, researchers have suggested factors that may be predictors of optimal retention. The use of ancillary support services, defined as any type of service that offers support to the individual (e.g. case management/social work, mental health, nutritional counseling, substance abuse treatment, legal services, housing, transportation, translation, HIV drug assistance programs, and child care), have been shown to be predictors of optimal care.[53-55,67-69] A study involving 2,647 patients receiving HIV primary care in Chicago, Illinois, found that patients with case management were 17% more likely to receive regular primary care compared to those without case management.[54] Researchers have also attempted to show that individuals who initiate HIV clinical care with non-HIV related comorbidity (e.g. diabetes, hypertension, renal disease, etc.) are more likely to retain in care, but results have been inconclusive.[22,70]

Retention in Care and HIV clinical Outcomes

Researchers have recently studied the effects retention in care has on HIV clinical outcomes and have shown that poor retention is associated with worse health outcomes compared to optimal retention.[14,15,21,22,24,28,41] Individuals who are poorly retained in care

are less likely to obtain a VL suppression[24,25,45,47,48], more likely to be hospitalized[65], more likely to acquire an ADI[27], and more likely to die[27-29,47] compared to those individuals who have optimal retention. From a public health standpoint, poor retention has been shown to increase the risk of antiretroviral resistance, decrease immune function, increase health care costs associated with increases in hospitalizations and emergency room use, and increase risky sexual behavior.[14,31]

Reducing the VL and maintaining VL suppression has become a major priority in the management of HIV as this reduces the infectivity of the individual living with HIV, thereby reducing the risk of transmission to others.[24,29,31] Individuals who do not maintain optimal retention in care have a difficult time obtaining suppressed VLs and those who do acquire a VL suppression are more likely to rebound to VL failure.[24] Mugavero et al. introduced a novel approach to observing VL over time; viremia copy-years, which is defined as the number of copies of HIV-1 RNA per ml per year circulating in plasma and integrated over the number of years from sero-conversion.[24,71] The authors hypothesized that early optimal retention in care predicts shorter time to VL suppression and lower cumulative VL burden. The authors were interested in how retention in care affected time to suppression of plasma HIV RNA <50 copies per milliliter and cumulative VL burden (viremia copy-years), a time-varying measure. In this study, the 676 individuals diagnosed with HIV between 2007 and 2010 were recruited and followed for 2 years to observe time to VL suppression and cumulative VL. For the time to VL suppression analyses, the authors measured early retention in care as a time-varying count of "no show" visits, and for the evaluation of 2-year viremia copy-years, the authors employed visit adherence, the proportion of scheduled visits that were attended.

The authors categorized visit adherence into three groups: 1)0% – 79%, 2) 80% – 99%, and 3) 100%. Twenty-five percent of the individuals had 2 or more "no show" visits, and 63% achieved VL suppression in a median of 308 days from entry in to care. In the Cox proportional hazards analysis, individuals with multiple "no show" clinic visits experienced significantly longer time to VL suppression (Hazard Ratio: 0.84; 95% Confidence Interval = 0.76 to 0.92). In multivariable linear regression, visit adherence was independently associated with a lower cumulative VL burden.[24]

Clinicians and researchers have focused most of their attention on the relationship between poor retention and VL suppression. There is a paucity of research on the relationship between retention and viral load rebound as well as the clinical progression of HIV disease. In 2007, Park et al. published an observational study where they observed the effect missed clinic visits had on clinical HIV progression. From January 1998 to December 2004, the authors included 387 individuals infected with HIV and seeking care in a tertiary referral hospital in Seoul, South Korea in the study and followed them for at least 1 year after the initiation of HAART. The authors defined retention in care as the number of missed clinic appointments and as the total cumulative number of days elapsed between a missed clinic visit and the next clinic visit summed over the follow-up period. Employing Cox proportional hazard models, the authors analyzed the relationship between missed clinic visits and the occurrence of new ADIs or death. Of the 387 individuals recruited for the analysis, 34% and 8% missed one or two appointments or three or more appointments respectively. New ADIs occurred in only 10% of the sample while a total of 8 died in the period of follow-up. Park et al. demonstrated that as the number of missed clinic visits and cumulative elapsed time increased, the hazard of progressing to a new ADI or death was 1.54 and 1.23, respectively. Although the sample size was small and the follow-up time was

short, the authors were able to show how missing scheduled appointments can dramatically affect the clinical management of HIV, causing the acquisition of new ADIs and death.[27]

Giordano employed a much larger medical chart review study (n= 2,619) to assess the relationship among visit constancy, a change in $CD4^+$ cell counts, a change in VL, and survival. The authors restricted their study to only men living with HIV who were listed in the VA Immunology Case Registry. The follow-up for the analyses began a year after the index visit and ended at death or the end of the study period. The authors categorized the patients by the number of 3 month intervals in the year in which they had a primary care visit after their initial visit. A dose response relationship was found for visit constancy, significantly affecting $CD4^+$ cell count, VL, and survival. The published study was significant as the researchers suggested that patients living with HIV should seek care at least once every three months as opposed to previous guidelines suggesting every 6 months.[22]

Researchers have suggested that optimal retention may reduce HIV transmission, which carries a significant public health benefit.[31] Metsch et al., in a longitudinal study showed that patients who had received HIV primary medical care at least 3 times in the preceding 6 months were significantly less likely to engage in unprotected vaginal or anal intercourse with HIV uninfected or unknown status partners in the preceding month.[31] This finding is extremely important as retention in care can be used as a prevention method to reduce the incidence of HIV as approximately 56,000 new HIV cases are identified each year in the U.S.[11,72]

Conclusion: Where are we now and what this dissertation proposes to add?

Retention in HIV medical care has become a significant topic among individuals living with HIV and deserves serious attention by both providers and public health agencies. It has been consistently shown by researchers, that patients in regular care are much more

likely to have better health outcomes, including VL suppression, than patients not in regular care. It is pertinent, at a programmatic and policy level, to identify and understand the factors beyond demographic characteristics that are related to poor retention in care, followed by an assessment of factors that can be addressed.[14] If poor retention is truly the most basic predictor of health outcomes, it is pertinent for resources and funds to be set aside for interventions devoted to preventing poor retention.[14]

Retention in care studies are fairly easy to employ as these studies may rely heavily on medical chart reviewing and no physical interaction with subjects and this advantage allows retention in care studies to be relatively inexpensive.[15] The way retention in care is measured varies and often depends on the data available to the researchers and clinicians as well as the reason for measuring retention. A major disadvantage with retention in care studies is the definition of retention. Unfortunately, there is no gold standard when it comes to defining retention in care, which makes comparison of studies difficult. To our knowledge, studies where a rigorous study has been conducted comparing multiple retention methods is rare.[43] This may in part be because of the complex nature involving longitudinal follow-up.

There is a strong need for more longitudinal studies which assess how retention changes over time and how sporadic to poor retainers are re-engaged into care. Although predictors of poor retention have been established in most studies, future studies should continue to observe factors outside the normal socio-demographic characteristics, as there still may be factors that play a role in optimal or poor retention, and also understanding how retention over time impacts the disease progression.

It is important to have consistent measurements of retention, but this will require making decisions on whether to focus on missed appointments or the number of completed

visits within a specified time period in order to capture retention in care.[14] It is also important for researchers to consistently define a completed clinic visit; whether it includes only HIV primary care visits or all types of medical visits. This consistency will assist in the comparison of multiple studies.

The dissertation plans to tackle some of the issues described in the retention in HIV medical care literature as well as add important findings to the current literature. Since defining retention in care varies among studies and there is currently no study that has analytically compared multiple retention methods, the dissertation plans to compare multiple methods to determine the most appropriate method in defining retention, by determining their ability to predict viral suppression. The dissertation also hopes to add more predictors of poor to optimal retention to the current literature. It is inconclusive how non-HIV related comorbidities impact retention over time. Lastly, the dissertation plans to observe how poor retention over time impacts time to VL suppression and rebound. There are currently no studies that have observed the impact of poor retention on viral rebound among individuals who have achieved viral suppression.

Chapter Three

A Comparison Study of Methods for Measuring Retention in HIV Medical Care

Introduction

Retention in medical care among individuals living with HIV has become a major priority among HIV medical providers and public health researchers. Engagement in medical care is an important concept as it involves the process of an early diagnosis, linkage to care, initiation of antiretroviral therapy, and retention in HIV medical care.[11,12,15] It is critical for individuals living with HIV, who are linked to care, to maintain optimal retention as this maximizes viral suppression, reduces the risk of AIDS progression, and reduces the risk of HIV transmission.[22,24,27,31] According to the HIV Medicine Association guidelines, an enormous emphasis should be placed on retention to HIV medical care rather than just concentrating on adherence to HIV medications.[73]

Despite the importance of retention in HIV medical care, there has been limited research on this topic. Similar to adherence to HIV medication studies, the central concern for researchers and medical providers is how to best define retention.[15,74,75] Measuring retention in HIV medical care can be complex as the process includes multiple clinic visits which occur longitudinally over time.[15] Although multiple methods have been used in defining retention in HIV medical care, there is currently no standard preferred method. Researchers have suggested up to five different methods, each with their limitations on how to best measure retention in care.[14,15] A consistent definition of retention must be set in place in order to compare results across studies.

In spite of multiple researchers studying retention in care, rigorous study comparing different retention measurement techniques in order to determine the best method remains rare. Measurement of long-term retention can be complex as it requires a longitudinal assessment.[15] To date, most studies have only employed one measure of retention and have focused on short time periods (1-3 years).[13,16,21,22,28,38,39,43] Yehia et al recently published a study comparing three different retention measures, but focused on how each measure was correlated with one another. Understanding how each retention measure determines immunological and virological outcomes is essential as estimates show that approximately 20% of people living with HIV/AIDS (PLWHA) achieve viral load (VL) suppression and that this low percentage is largely due to poor retention.[11,12]

Modeling adherence to HIV medication studies, methods are validated and chosen based on their ability to predict virological outcomes.[74-76] To date, there has not been any study to observe multiple methods of retention to compare their ability to predict virological and immunological outcomes. The current study adds to the current research by comparing multiple measures of retention to HIV medical care. Using VL and $CD4^+$ cell counts as the clinical criterion, the purpose of this study is to determine each measure's ability to determine VL suppression and CD4+ cell count failure among PLWHA seeking HIV medical care at an academic infectious disease clinic.

Methods

Study Design

The purpose of this study was to determine retention in HIV medical care using three measurement techniques, and to compare their ability to predict VL suppression and $CD4^+$ cell count failure. In order to accomplish this objective, a retrospective cohort study employing a medical chart review was conducted at an academic infectious disease clinic in

Kentucky (KY). Individuals who sought care between January 1st, 2003 and May 1st 2011 were considered eligible for this study, and were followed until December 31st, 2011. January 1st, 2003 was chosen as the start date, since the care clinic integrated an electronic database during this time period, and May 1st, 2011 was chosen to be the recruitment end date, as this would allow individuals to have had at least six months of follow-up time at the end of the study period (allowing an individual to have a follow-up viral load and $CD4^+$ cell count measurement). During the follow-up period, individuals were followed until the end of the study period (December 31st, 2011), death, or move out of service region. The study was approved by the University of KY Institutional Review Board.

Study Site

Individuals diagnosed with HIV and referred to the Bluegrass Care Clinic (BCC) for medical care were considered for inclusion in the study. The BCC is a multi-disciplinary HIV care clinic located in an urban area in KY. The BCC is the largest of four HIV care providers in a 63 county area in KY federally funded through the Ryan White HIV/AIDS Treatment and Modernization Act of 2006, and non-federal funds through the Commonwealth of KY. The BCC provides expert medical care by physicians, nurses, pharmacists, and other clinicians trained to deal with the complex management of a variety of infectious diseases, including HIV and related conditions. The BCC is home to approximately 1,050 active patients, which includes those living with HIV disease and approximately 50% of the patient population lives in rural areas in KY.

Study Population and Eligibility

Data for this study were abstracted from the HIV Lab Tracker™, an electronic database located at the BCC. The HIV Lab Tracker™ is an advanced electronic database solution for managing patients living with HIV. The lab tracker encompasses a comprehensive list of information for each patient, which includes demographic, laboratory, medication, and clinical data.

Individuals were considered for the study if they were diagnosed with HIV before or during the study period and were 18 years of age or older. To obtain the individuals that met the initial criteria, individuals were queried in the database on the following criteria: 1) HIV diagnosis date (May 1st, 2011 and earlier) and 2) Age (≥ 18 years). The query resulted in 1,485 individuals who were pulled from the database and were initially eligible for the research study. Individuals were included in the study if they sought HIV medical care at the BCC during the specified time period, had at least two completed clinic visits (intake visit and subsequent clinic visit), had at least 6 months of follow-up time, and had the appropriate dates recorded (clinic visits, HIV diagnosis, AIDS diagnosis, VL and CD4+ cell count dates). Of the 1,485 individuals pulled from the database, 1,358 individuals were included for follow-up (Figure 3.1).

The individuals included in the study were followed at 6 month intervals from their initial start date to the end of the follow-up period. Individuals, whose initial start date came before the beginning of the study period (January 1st 2003), were followed from their first completed clinic visit in the time frame.

During each 6 month follow-up interval, the following information was observed: the number of completed clinic visits, laboratory results (i.e. VL and $CD4^+$ cell counts), acquisition of new infections/diseases (e.g. AIDS, opportunistic infections, non-HIV related comorbidities), number of hospitalizations, and/or death.

Baseline demographic and clinical data were abstracted from the HIV Lab Tracker ™ database for those individuals that were included in the study. Demographic information included date of birth, sex, race/ethnicity, marital status, country of origin (U.S. born/Foreign born), employment status, insurance status (private, Medicare, Medicaid, and none), federal poverty level, history of tobacco use (yes/no), history of alcohol use (yes/no), history of illicit drug use (yes/no), and HIV transmission category (Men who have Sex with Men (MSM), Heterosexual contact, Injection Drug Users (IDU), and other). For the transmission category, 'other' consisted of transfusion, hemophilia, and unknown. Poverty level was defined using the federal poverty level guidelines and was dichotomized into <100% below the federal poverty level (income <$10,000) and >100% below the federal poverty level. Income was not complete for most patients, so poverty level was ascertained from the income values that were present for patients as well as the programs patients were enrolled in as these are based on their poverty level. For descriptive purposes, race/ethnicity was defined as Non-Hispanic (NH) White, NH Black, Hispanic, and other. Due to the small numbers of the non-white group, race was dichotomized into NH white versus non-white for the bivariate and multivariate analyses.

Baseline clinical characteristics ascertained from the medical records included $CD4^+$ cell counts (cells/μl), VLs (copies/ml), OI diagnoses, AIDS diagnoses, sexually transmitted infections, comorbidities, any hospitalizations, and receipt of HAART. An individual was diagnosed with AIDS if they had one of the following: a $CD4^+$ cell count <200, a $CD4^+$ cell

count percentage < 14, or one of the 26 AIDS defining Illnesses (ADIs).[77] A concurrent AIDS diagnosis was defined as an AIDS diagnosis within 30 days of an HIV diagnosis. VL had a wide variation in its distribution and was greatly skewed, therefore, VL was log transformed and observed as log copies/ml for descriptive purposes. Patients that initiated care with an AIDS diagnosis and had a missing CD4+ cell count result was given a value of 150 and a value of 250 if they had a missing CD4+ cell count and initiated care without an AIDS diagnosis. Death was ascertained using the social security death index and the EMR. For patients that were lost to follow-up or moved out of the service region, the social security death index assisted in determining the date of death for those patients, if necessary.

Retention Measures

The current guidelines set by the U.S. Department of Health and Human Services (DHHS) for adolescents and adults with HIV states that primary care visits should be made by newly diagnosed persons at least every 3 to 4 months until initial patient evaluation is completed and stable clinical and immunological status is achieved for 2 to 3 years. Thereafter, at least one visit every six months is recommended for monitoring health outcomes.[23] To determine the best method in defining retention in care, three measures of retention were observed during this study: 1) visit constancy; 2) gaps in care; and 3) the HRSA performance measure. Visit constancy was observed as the proportion (%) of 6-month intervals with at least one clinic visit during the study period that the patient was a member of the cohort. Patients were classified into 4 groups: Optimal (100%), Suboptimal (99-75%), Sporadic (74-50%), and Poor (<50%).[21] Gaps in care were defined as the time (in months) between two consecutive clinic visits. Patients were classified as ever having a gap <12 months or ≥ 12 months. The last retention measure involved a measurement described and used by HRSA and included in the National HIV/AIDS Strategy (NHAS).[59] The HRSA

performance measurement was defined as having completed at least 2 clinic visits separated by 3 or more months within a 12-month period. To calculate this measure, each patient had their follow-up broken into 12-month intervals. For each interval, the HRSA performance measure was observed, and the proportion of 12-month intervals where the HRSA performance measurement criteria was met was calculated.[58] A clinic visit was defined as an HIV medical outpatient care visit. Since laboratory tests were ordered by the HIV care physicians during each clinic visit, VL and CD4+ cell count measurements were used as surrogate clinic visits.

Outcome Measures

At the end of the follow-up period, each individual's final VL and $CD4^+$ cell count was assessed. If an individual failed to acquire a VL or $CD4^+$ cell count at the last 6 month interval, the measurement closest to the end of the study period was chosen. VL is the standard measurement for HIV treatment success or failure and is a surrogate measure for medication adherence, so the primary outcome was to understand how well retention discerns between those individuals who have a suppressed VL and those who do not. VL suppression was defined as achieving a VL of <50 copies/ml.[24,78] The secondary outcome was $CD4^+$ cell count failure and was defined as a 10% decrease in counts from baseline.[79]

Statistical Analyses

Data were analyzed using the Statistical Analysis Software SAS version 9.3.; SAS Institute; Cary North Carolina. Descriptive statistics were employed for the entire study sample. Means and standard deviations were calculated to describe the continuous variables and frequencies and percentages were used to describe the categorical variables. For the bivariate and multivariate analyses, the sample was restricted to those individuals who had a follow-up VL and/or $CD4^+$ cell count (Figure 3.1). Bivariate analyses observed

differences between groups and VL suppression and CD4+ cell count failure. To determine differences in means between those with and without VL suppression, independent two-sample *t* tests were used. χ^2 tests of independence were used to determine significant differences between categorical variables and VL suppression.

To determine the retention measure that most accurately predicted virological and immunological outcomes, receiver operating characteristic curves (ROC) were produced. An ROC curve is a plot of sensitivity as function of (1-specificity) for all possible cutoffs.[80,81] Logistic regressions were employed to obtain the ROC curves for visit constancy, gaps in care, and the HRSA performance measure. The purpose was to determine which measurement most accurately discriminated between those individuals who suppressed their VL and those who did not. The same steps were performed for discerning between those with a CD4+ cell count failure or not. The area under the curve (AUC) estimates was produced with each ROC curve, and the AUC measure was used to determine the ability of each retention measure to correctly classify those individuals with a suppressed VL and those without a suppressed VL and the same for cell count failure.[80] Separately, each retention measure's AUC was compared to chance (AUC = 0.5), and χ^2 tests were used to determine whether the retention measure's AUC was significantly different from chance. An AUC that was significantly greater than chance was considered a useful measure in correctly discerning between the different groups. Each retention measure was then compared to each other to determine the best measure in predicting the outcomes.

Multiple logistic regression models were performed for each retention measure (visit constancy, gaps in care, and HRSA) to determine the relationship between each retention measure and the virological and immunological outcomes while controlling for confounders and other risk factors. Variables with a *p*-value ≤0.15 in the bivariate analyses

were considered for inclusion into each regression model. Variables were included in the model as confounders based on previous literature. Variables that were initially included in the models that did not appear to have an effect on the outcome or confound the relationship between retention and the outcome were removed from the model. Interactions between each variable and the retention measure were tested. There was a significant interaction between initial CD4+ cell count and initial VL. The Hosmer and Lemeshow goodness of fit tests were used to determine each models fit and Akaike Information Criteria (AIC) was used to determine which fitted model was best.

The multiple logistic regression, modeling the probability of not obtaining VL suppression, included race, insurance type, initial $CD4^+$ cell counts and VLs interaction, concurrent HIV/AIDS diagnosis, year of HIV diagnosis, and HAART. The logistic regression, modeling the probability of CD4+ cell count failure, included race, insurance type, initial CD4+ cell counts and VLs, concurrent HIV/AIDS diagnosis, year of HIV diagnosis, and HAART.

Results

Demographic and Clinical Characteristics

Of the 1,358 individuals included in the analysis, the mean age at the start of the study period was 38 ± 10 years, 81.2% (n = 1,102) were male, and 70.2% (n= 952) were Non-Hispanic White (Table 3.1). A large proportion of the population entered clinic care living below the poverty level (48.9%), with approximately 42.6% (n= 569) having no insurance (Table 3.1).

Over half of the population acquired an AIDS diagnosis (53.3%) throughout the study period, with 25.1% of them having a concurrent diagnosis. Approximately 28.3% of the individuals initiated care with a $CD4^+$ cell count <200 cells/μl meaning that these individuals entered the study at a much advanced stage of disease. A total of 1,166 (85.9%) patients had initiated HAART (Table 3.1).

Among the 1,358 patients included in the study, the mean years of follow-up were 5.75 ± 2.65 years (median = 6.20) and the patients completed a mean of 39.6 ± 39.8 clinic visits (median = 28.0). At the end of the follow-up period, 797 (59%) patients had a follow-up VL recorded, but only 57.8% of those achieved a suppressed VL. Non-whites, individuals living below the poverty level, those uninsured or on Medicaid, non-concurrent diagnosed individuals, and those with CD4+ cell counts <200 cells/μL were less likely to achieve a suppressed VL compared to their counterparts (Table 3.2).

For CD4+ cell count failure, 824 (61%) patients that a follow-up measurement recorded during the study period, and approximately 26% of the patients had an immunological failure. Patients with Medicaid or no insurance were more likely to have a failure compared to those with Medicare and private insurance. Immunological failure was also more likely to be found in those patients without a concurrent diagnosis, without HAART, and those with higher CD4+ cell counts and VLs at initiation (Table 3.2).

Retention in Care Measures

Table 3.3 presents the retention in care measurements. Overall the average percentage of 6-month intervals with at least one visit (visit constancy) was 77.6 ±29.9% (median = 94.1), with 48.6% having at least one visit every six months (optimal retention) over the 9-year study period. For the HRSA performance measurement, the average percentage of 12-month intervals where the criteria was met was 77.2 ±29.7% (median =

88.9) among the entire study sample. However, only 592 (43.6%) patients met the HRSA criteria every 12-month period they were in the study. The longest time between consecutive visits was collected for each patient in the study. The average time between two consecutive visits for the sample was 8 ±9.1 months (median = 5.5). Throughout the study period, 15.5% of the patients had at least one interval greater than 12 months.

VL suppression was more likely among those patients who met each retention criteria (Table 3.3). For the HRSA performance measure, the mean percentage of intervals with at least two visits separated by 3 or more months was higher for those with a suppressed VL compared to those without a suppressed VL (88.8% versus 78.0%, $p<0.0001$). Approximately 61% of the individuals who met the HRSA criteria 100% percent of the time had a suppressed VL compared to just 55.6% of those who did not meet the criteria. Patients who had an interval greater than 12 months were less likely to achieve a suppressed VL compared to those with intervals less than 12 months (43.3% versus 61.0%, $p = 0.0001$). On average, patients with a suppressed VL had more 6-month intervals with at least one visit compared to those who did not have a suppressed VL (93.5% versus 69.9%, $p <0.0001$). Dividing visit constancy into categories, there was a clear dose response for individuals achieving a suppressed VL. Approximately 74% of optimal retainers achieved a suppressed VL compared to 58%, 36.9%, and 5.4% for suboptimal, sporadic, and poor retainers, respectively ($p<0.0001$).

CD4+ cell count failure was more likely among those patients that did not retain fully in care. The mean percentage of 12-month intervals where the HRSA criteria was met was lower for those with a failure compared to those without a failure (79.1% versus 84.9%, $p = 0.001$). The average time between two consecutive visits was higher for those with a CD4+ cell count failure compared to those without a count failure (11.4 versus 8.4

months, p = 0.001). On average, patients with a CD4+ cell count failure had less 6-month intervals with at least one visit compared to those who did not have a failure (79.1% versus 85.0%, p = 0.004) (Table 3.3).

Tables 3.4 and 3.5 present the ROC statistics for predicting VL suppression and CD4+ cell count failure, respectively. For VL suppression, the AUCs were larger for visit constancy (0.736) than for the HRSA performance measure (0.603), and gaps in care (0.532). Compared to chance (AUC = 0.5), gaps in care was the only retention measure that was not significantly greater than chance (p=0.133), suggesting that gaps in care is not a good measure in discerning between VL suppressers and non-suppressers (Table 3.4). Figure 3.1 presents the ROC curves for the retention measures, and it shows that visit constancy outperforms gaps in care and the HRSA performance measure (p<0.0001). For determining CD4+ cell count failure, the three retention measures did not perform well in determining those patients with cell count failure (Figure 3.2). There were no differences in the AUCs among the three retention measures, although each measure was significantly different from chance (Table 3.5).

Multiple logistic regressions were performed to determine the association of each retention measure with viral suppression and CD4+ cell count failure, while controlling for the confounding variables. While controlling for the variables, gaps in care and visit constancy were significantly associated with viral suppression (Table 3.6). Patients with gaps >12 months had greater odds of not achieving viral suppression compared to those with gaps <12 months (Odds Ratio (OR) = 1.88; 95% Confidence Interval (CI) = 1.26, 2.80). Compared to optimal retainers, suboptimal (OR = 2.09; 95% CI = 1.44, 9.41), sporadic (OR = 5.50; 95% CI = 3.20, 9.41), and poor retainers (OR = 44.2; 95% CI = 17.0, 114.6) were at greater odds of not suppressing VLs (Table 3.6). There were no significant interactions

between the variables and retention, but there was a significant interaction between initial VL and CD4+ cell counts, suggesting that lower CD4+ cell counts and higher VLs were at greater odds of failing to have viral suppression (data not shown). While controlling for the confounding variables, the HRSA performance measure, gaps in care, and visit constancy were all significantly associated with CD4+ cell count failure (Table 3.7). Patients that did not meet the HRSA performance criteria were 1.53 times the odds of failure compared to those where the criteria was met. Compared to optimal retainers, sporadic and poor retainers had greater odds of cell count failure at 1.85 and 1.84, respectively.

Discussion

A major issue with retention in care studies is determining how to best define retention in HIV outpatient medical care among PLWHA. It has been suggested that there are at least five different ways to measure retention and currently no gold standard is in place, which makes comparison of studies difficult.[14,15] There is still a debate on which retention measure to use. The purpose of this study was to compare three different measures of retention by determining their ability to predict VL suppression and CD4+ cell count failure. For VL suppression, it was found that visit constancy outperformed the HRSA performance measure and gaps in care in regards to discerning between those patients with and without VL suppression. For CD4+ cell count failure, it was found that all three retention measures performed poorly when determining failure.

The means for HRSA measure and visit constancy were similar among the study sample, with approximately 77.2% of all 12-month patient-care intervals having met the HRSA criteria and approximately 77.6% of all 6-month patient-care intervals having at least one visit. For gaps in care, we were able to show that the longest average time between two consecutive visits was approximately 8 months. Our study is among the few studies to

employ a relatively long follow-up period to measure retention in care, with an average follow-up time of 5 years among the entire cohort.[82,83] Yehia et al. in 2012 conducted a similar study, comparing the HRSA performance measure, visit constancy and gaps in care measures among a cohort of adults enrolled in an HIV Research Network (HIVRN). Using 3-month intervals to estimate visit constancy and an average follow-up time of 35.5 months, 73% of all 3-month intervals had at least one visit and 75% of all 12-month intervals met the HRSA measure.[43] In our cohort, the mean percentages were slightly higher than the Yehia et al. cohort. Reasons for this could be the cohort chosen for the study (Ryan White population versus HIVRN network), the sample size (1358 versus 17,425), or the choice in patient-care intervals (6 months versus 3 months).

In our study, approximately 44% of the cohort met the HRSA criteria 100% of the time. The HRSA performance measure is a measure created and endorsed by HRSA and described in NHAS. The measure was created to be used as an indicator for providers receiving Ryan White CARE Act funding and is typically restricted to just 12 months.[15,58] We followed individuals over a 9 year period to calculate the percentage of years where the criteria were met. Until recently, the HRSA measurement was not observed in most retention studies[38,39,43], but Hall et al. conducted a study using HIV surveillance data from 13 areas in the U.S. and showed that approximately 45% of PLWHA had met the HRSA criteria.[39] Our results were similar to theirs.

Observing visit constancy among all the patients in the study, only 49% had optimal retention (all 6-month patient-care intervals had at least one clinic visit) while approximately 12% had poor retention (<50% retention). The retention rate among our study sample is rather low and falls below the goal set by NHAS to increase the proportion of clients who are in continuous care from 73% to 80%. In regards to gaps in care, only

15.5% of the cohort had one or more gaps >12 months, which is lower than what most studies have reported.[43,51,84] The data strongly suggests that significant energy needs to be put toward increasing the number of individuals optimally retained in care and understanding the factors that may impact retention among this cohort is a key component. Further studies should be conducted and strategies should be set in place to re-engage those that are lost to follow-up.

The measures of retention to medical care calculated in this study were compared to one another by employing methods described in adherence to HIV medication studies.[74-76] Measures were compared based on their ability to predict VL suppression since VLs are normally used as surrogate measures for medication adherence and determining how well a patient is managing their disease.[74,79] It was shown that visit constancy had the highest AUC compared to the other two measures, suggesting a higher chance of discerning VL suppression. In 2001, Liu et al conducted a similar study, but used ROC curves to determine the relationship between medication adherence and VL suppression. The average AUC calculated for the adherence measures was 77.5%.[76] The AUC calculated for visit constancy in the current study was 73.6% which suggests that visit constancy may be potentially used as a surrogate measure for measuring adherence to medication for programs that do not have the resources to conduct medication adherence studies. Future studies should be conducted to determine the relationship between medication adherence and retention to medical care, in particular visit constancy.

Only 58% of the patient cohort had achieved VL suppression by the end of follow-up, but of those approximately 74% were optimal retainers. The logistic regressions suggested that poor retention in care greatly hinders a patient from achieving a suppressed VL. While controlling for the confounding variables, gaps in care and visit constancy were

the only measures significantly associated with the failure to achieve VL suppression. Comparing AICs, visit constancy had the better fitted model suggesting it should be considered the best retention in care measure. With visit constancy, the individuals that were suboptimal, sporadic, and poor retainers had much greater odds of VL failure compared to optimal retainers. This is an interesting finding as there appears to be a dose-response, suggesting that an individual needs to maintain 100% retention in order to achieve adequate VL suppression. The results have major implications on the health of the individual as well as public health prevention efforts. Individuals that are not retaining in care are missing opportunities to suppress their VLs which in turn puts them at risk for transmitting the virus to others.

There are limitations to this study. The study was an observational, retrospective cohort study and subject to potential uncontrolled confounders that could not be identified and studied. Medical chart review was employed to capture the study information, but not all patients had complete information in their records. Patients with missing VL or CD4+ cell count information were excluded from the study. Excluding patients dues to missing information may introduce bias and reduce the power of the study. However, there were no significant differences in demographic and clinical characteristics between those that were excluded from the analysis.

The percentage of patients missing VL and CD4+ cell counts in this study is a concern. The DHHS panel on antiretroviral guidelines for Adults and Adolescents recommends regular monitoring of disease status and treatment response with CD4+ cell counts and VLs every 3-4 months, but once VLs have been suppressed CD4+ cell counts may be measured less frequently (6-12 months).[23] The majority of the patients in the study were on HAART, and a percentage of them did not have laboratory tests done. Retention in care

seems to play a role in this scenario, as even after individuals have reached viral suppression they should continue to visit the clinic and have lab work conducted to ensure they do not rebound to viral failure.

Another limitation to this study was the definition for clinic visits. In the retention in care literature, it is debated as to what constitutes a clinic visit.[14,15] For this study, a clinic visit was defined as an HIV medical care visit (outpatient) and laboratory results (i.e. VL or $CD4^+$ cell counts) were considered surrogate measures. To be consistent with other studies, medical care visits with a non-HIV care provider were not included in the clinic visit definition. This limitation could lead to a misclassification bias as individuals who seek medical care from non-HIV providers may be classified as poor retainers, therefore overestimating non-retainers in the study. There is the potential for selection and misclassification bias as individuals were removed from the study when they did not have a follow-up visit after their initial visit or at least 6 months of follow-up. Removing these individuals from the analysis may underestimate the number of poor retainers seeking medical care at the BCC. It was not feasible to find out if these individuals were seeking HIV medical care at other clinics. We do not believe patients would seek care at other clinics often because most of the patients relied on funding from the clinic for medication and patient care and other options for HIV/AIDS care in their region may be limited.

Finally, medication adherence was not observed or evaluated in this study. Studies have observed the impact medication adherence has on viral suppression as well as viral rebound, and have suggested that patients that are not at least 95% adherent to their medications are more likely to have virological failures. Medication adherence is on the causal pathway between retention in care and VL suppression, but the purpose of this study was to establish the relationship between retention and VL suppression. It may be

concluded that medication adherence is the driving force behind viral suppression, but Giordano et al were able to show that poor retention in care and poor medication adherence were highly correlated therefore it seemed appropriate to use retention in care as a surrogate measure.[85] Also obtaining medication adherence is difficult. As with the patient population at the BCC, patients may obtain their medications from multiple pharmacies, making it difficult to track medication usage. If a centralized pharmacy were available for this population, medication adherence may have been accurately assessed.

Conclusion

When defining retention to HIV medical care, our study indicated that visit constancy may be the most appropriate measure. Visit constancy outperformed HRSA and gaps in care predicting VL suppression and was significantly associated with CD4+ cell count failure. It was shown that approximately 42% of the patients in the study did not achieve viral suppression and 26.2% had a CD4+ cell count failure. Poor retention may have a role in the failure to maintain successful management of HIV as only 48.6% of the patient cohort was able to maintain optimal retention. Interventions should be set in place to increase the number of optimal retainers and re-engage those individuals that have completely fallen out of care.

Table 3.1 Socio-demographic and Clinical Characteristics among the Patients Seeking HIV Medical Care: 2003 - 2011

	Total n (%)
Total	1358 (100)
Sex	
Female	256 (18.9)
Male	1102 (81.2)
Race	
White Non-Hispanic	952 (70.2)
Black Non-Hispanic	273 (20.1)
Hispanic	123 (9.1)
Other	8 (0.6)
Age at Baseline	
≤24 yrs	136 (10.0)
25 - 34 yrs	362 (26.7)
35 - 44 yrs	504 (37.1)
>44 yrs	356 (26.2)
Age mean (std)	38.2 (10.05)
Mode of Transmission	
Heterosexual	385 (28.4)
IDU	122 (9.0)
Other	72 (5.3)
MSM	777 (57.3)
Employment Status	
Employed	501 (44.8)
Unemployed	402 (36.0)
Other	215 (19.2)
Poverty Level	
Below Poverty Level	662 (48.8)
Above Poverty Level	446 (32.8)
Missing	250 (18.4)
History of Tobacco Use	
Yes	686 (50.5)
No	672 (49.5)
History of Illicit Drug Use	
Yes	365 (26.9)
No	993 (73.1)

Table 3.1 continued

	Total
Insurance Type	
No Insurance	569 (42.6)
Medicaid	212 (15.9)
Medicare	211 (15.8)
Private	344 (25.8)
Concurrent Diagnosis	
Concurrent	341 (25.1)
Non-Concurrent	1017 (74.9)
History of AIDS Diagnosis	
Yes	724 (53.3)
No	634 (46.7)
History of Hospitalizations	
Yes	738 (54.3)
No	620 (45.7)
Hepatitis C	
Yes	172 (12.7)
No	1186 (87.3)
HAART Use	
Yes	1166 (85.9)
No	192 (14.1)
CD4+ Cell Counts	
<200	384 (28.3)
>200	974 (71.7)
Initial Viral Load mean log copies (std)	6.75 (3.05)

Table 3.2 Socio-demographic and Clinical Characteristics by Virological and Immunological Outcomes among the Patients Seeking HIV Medical Care: 2003 - 2011

	Suppressed Viral Load (n = 797)			CD4 Failure (n = 824)		
	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p
Total	461 (57.8)	336 (42.2)		216 (26.2)	608 (73.8)	
Sex			0.15			0.43
Female	79 (52.7)	71 (47.3)		44 (28.8)	109 (71.2)	
Male	382 (59.0)	265 (41.0)		172 (25.6)	499 (74.4)	
Race			<0.0001			0.26
Non-White	84 (42.9)	112 (57.1)		60 (29.3)	145 (70.7)	
White	376 (62.7)	224 (37.3)		156 (25.2)	462 (74.8)	
Age at Baseline			0.24			0.54
≤24 yrs	31 (54.4)	26 (45.6)		18 (30.5)	41 (69.5)	
25 - 34 yrs	101 (52.1)	93 (47.9)		59 (28.9)	145 (71.1)	
35 - 44 yrs	190 (60.1)	126 (39.9)		83 (25.5)	242 (74.5)	
>44 yrs	139 (60.4)	91 (39.6)		56 (23.7)	180 (76.3)	
Mode of Transmission			0.47			0.15
Heterosexual	131 (59.8)	88 (40.2)		60 (26.3)	168 (73.7)	
IDU	39 (50.0)	39 (50.0)		28 (35.9)	50 (64.1)	
Other	22 (55.0)	18 (45.0)		12 (30.0)	28 (70.0)	
MSM	269 (58.5)	191 (41.5)		115 (24.1)	362 (75.9)	
Employment Status			0.01			0.75
Employed	203 (65.5)	107 (34.5)		78 (24.5)	240 (75.5)	
Unemployed	131 (53.9)	112 (46.1)		69 (27.3)	184 (72.7)	
Other	91 (65.5)	48 (34.5)		36 (25.2)	107 (74.8)	
Poverty Level[a]			<0.0001			0.08
Below Poverty Level	207 (53.2)	182 (46.8)		120 (29.6)	285 (70.4)	
Above Poverty Level	203 (68.1)	95 (31.9)		67 (22.2)	235 (77.8)	
Missing	51 (46.4)	59 (53.6)		29 (24.8)	88 (75.2)	
History of Tobacco Use			0.05			0.6
Yes	226 (54.6)	188 (45.4)		116 (27.0)	314 (73.0)	
No	235 (61.4)	148 (38.6)		100 (25.4)	294 (74.6)	
History of Illicit Drug Use			0.10			0.14
Yes	103 (52.8)	92 (47.2)		62 (30.1)	144 (69.9)	
No	358 (59.5)	244 (40.5)		154 (24.9)	464 (75.1)	

Table 3.2. Continued

	Viral Suppression			CD4 Failure		
	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p
Insurance Type			0.003			0.03
No Insurance	150 (52.6)	135 (47.4)		86 (28.4)	217 (71.6)	
Medicaid	68 (50.8)	66 (49.3)		46 (33.6)	91 (66.4)	
Medicare	94 (61.8)	58 (38.2)		33 (21.2)	123 (78.9)	
Private	149 (66.8)	74 (33.2)		49 (21.8)	176 (78.2)	
Concurrent Diagnosis			0.04			0.01
Concurrent	129 (64.2)	72 (35.8)		40 (19.3)	167 (80.7)	
Non-Concurrent	332 (55.7)	264 (44.3)		176 (28.5)	441 (71.5)	
History of AIDS Diagnosis			0.01			0.23
Yes	249 (54.0)	212 (46.0)		133 (27.8)	346 (72.2)	
No	212 (63.1)	124 (36.9)		83 (24.1)	262 (75.9)	
History of Hospitalizations			0.10			<0.001
Yes	274 (55.6)	219 (44.4)		161 (31.4)	352 (68.6)	
No	187 (61.5)	117 (38.5)		55 (17.7)	256 (82.3)	
Hepatitis C			0.19			0.1
Yes	54 (51.9)	50 (48.1)		36 (32.7)	74 (67.3)	
No	407 (58.7)	286 (41.3)		180 (25.2)	534 (74.8)	
HAART Use			<0.001			<0.001
Yes	449 (60.3)	296 (39.7)		185 (24.5)	571 (75.5)	
No	12 (23.1)	40 (76.9)		31 (45.6)	37 (54.4)	
CD4+ Cell Counts			0.001			0.006
<200	98 (48.3)	105 (51.7)		40(19.1)	170 (80.9)	
>200	363 (61.1)	231 (38.9)		176 (28.7)	438 (71.3)	
Initial Viral Load mean log copies (std)	6.16 (3.01)	6.94 (3.01)	<0.001	6.72 (2.90)	6.45 (3.07)	<0.001

Table 3.3. Retention in Care Measures by Immunological and Virological Outcomes among the Patients Seeking HIV Medical Care: 2003 - 2011

	Total (n=1358)	Viral Suppression (n=797)			CD4+ Cell Count Failure (n=824)		
	n (%)	Yes n (%)	No n (%)	p-value	Yes n (%)	No n (%)	p-value
HRSA							
Mean %(std)	77.2 (29.7)	88.8 (14.6)	78.0 (25.8)	<0.0001	79.1 (23.4)	84.9 (21.0)	0.001
Yes	592 (43.6)	217 (60.6)	141 (39.4)	0.15	81 (22.1)	286 (77.9)	0.02
No	766 (56.4)	244 (55.6)	195 (44.4)		135 (29.5)	322 (70.5)	
Gaps in Care							
Mean months (std)	8.1 (9.1)	7.9 (6.1)	10.6 (11.9)	0.12	11.4 (12.4)	8.4 (8.4)	0.001
>12 months	210 (15.5)	61 (43.3)	80 (56.7)	0.0001	60 (40.8)	87 (59.2)	<0.0001
<12 months	1148 (84.5)	400 (61.0)	256 (39.0)		156 (23.0)	521 (77.0)	
Visit Constancy							
Mean %(std)	77.6 (29.9)	93.5 (11.9)	69.9 (30.3)	<0.0001	79.1 (23.4)	85.0 (23.6)	0.004
Optimal	660 (48.6)	301 (73.8)	107 (26.2)	<0.0001	90 (21.2)	334 (78.8)	0.002
Suboptimal	281 (20.7)	124 (58.2)	89 (41.8)		67 (31.0)	149 (69.0)	
Sporadic	158 (11.6)	31 (36.9)	53 (63.1)		22 (25.6)	64 (74.4)	
Poor	259 (19.1)	5 (5.4)	87 (94.6)		37 (37.8)	61 (62.2)	

Table 3.4. Receiver Operating Characteristic Curve Statistics for Detecting Viral Suppression

Variable	Area Under the Curve (AUC)	Standard Error	95% CI		p-value
			Lower Bound	Upper Bound	
Visit Constancy	0.736	0.017	0.702	0.77	<0.0001
HRSA Performance	0.603	0.02	0.563	0.642	<0.0001
Gap in Care	0.532	0.021	0.49	0.574	0.133

Note: p-values denote differences between each retention measure and chance using chi-square tests

Table 3.5. Receiver Operating Characteristic Curve Statistics for Detecting CD4+ Cell Count Failure

Variable	Area Under the Curve (AUC)	Standard Error	95% CI		p-value
			Lower Bound	Upper Bound	
Visit Constancy	0.573	0.022	0.531	0.615	0.001
HRSA Performance	0.577	0.022	0.533	0.620	0.001
Gap in Care	0.572	0.024	0.525	0.618	0.003

Note: p-values denote differences between each retention measure and chance using chi-square tests

Table 3.6. Multiple Logistic Regression of Viral Suppression by Retention in Care Categories

	Viral Load Failure					
	Yes n (%)	No n (%)	OR	95% CI	aOR	95% CI
HRSA HAB						
Yes	141 (39.4)	217 (60.6)	Ref		Ref	
No	195 (44.4)	244 (55.6)	1.23	(0.93, 1.63)	1.25	(0.92, 1.69)
Gaps in Care						
>12 months	80 (56.7)	61 (43.3)	**2.05**	**(1.42, 2.96)**	**1.88**	**(1.26, 2.80)**
<12 months	256 (39.0)	400 (61.0)	Ref		Ref	
Visit Constancy						
Optimal	107 (26.2)	301 (73.8)	Ref		Ref	
Suboptimal	89 (41.8)	124 (58.2)	**2.02**	**(1.42, 2.87)**	**2.09**	**(1.44, 3.04)**
Sporadic	53 (63.1)	31 (36.9)	**4.81**	**(2.93, 7.89)**	**5.5**	**(3.2, 9.41)**
Poor	87 (94.6)	5 (5.4)	**48.91**	**(19.34, 123.6)**	**44.2**	**(17.0, 114.6)**

Table 3.7. Multiple Logistic Regression of CD4+ Cell Count Failure by Retention in Care Categories

	CD4+ Cell Count Failure					
	Yes n (%)	No n (%)	OR	95% CI	aOR	95% CI
HRSA HAB						
Yes	81 (22.1)	286 (77.9)	Ref		Ref	
No	135 (29.5)	322 (70.5)	**1.48**	**(1.08, 2.04)**	**1.53**	**(1.09, 2.15)**
Gaps in Care						
>12 months	60 (40.8)	87 (59.2)	**2.30**	**(1.58, 3.35)**	**2.04**	**(1.37, 3.06)**
<12 months	156 (23.0)	521 (77.0)	Ref		Ref	
Visit Constancy						
Optimal	90 (21.2)	334 (78.8)	Ref		Ref	
Suboptimal	67 (31.0)	149 (69.0)	**1.67**	**(1.15, 2.42)**	**1.85**	**(1.24, 2.75)**
Sporadic	22 (25.6)	64 (74.4)	1.28	(0.75, 2.18)	1.3	(0.73, 2.32)
Poor	37 (37.8)	61 (62.2)	**2.25**	**(1.41, 3.60)**	**1.84**	**(1.08, 3.12)**

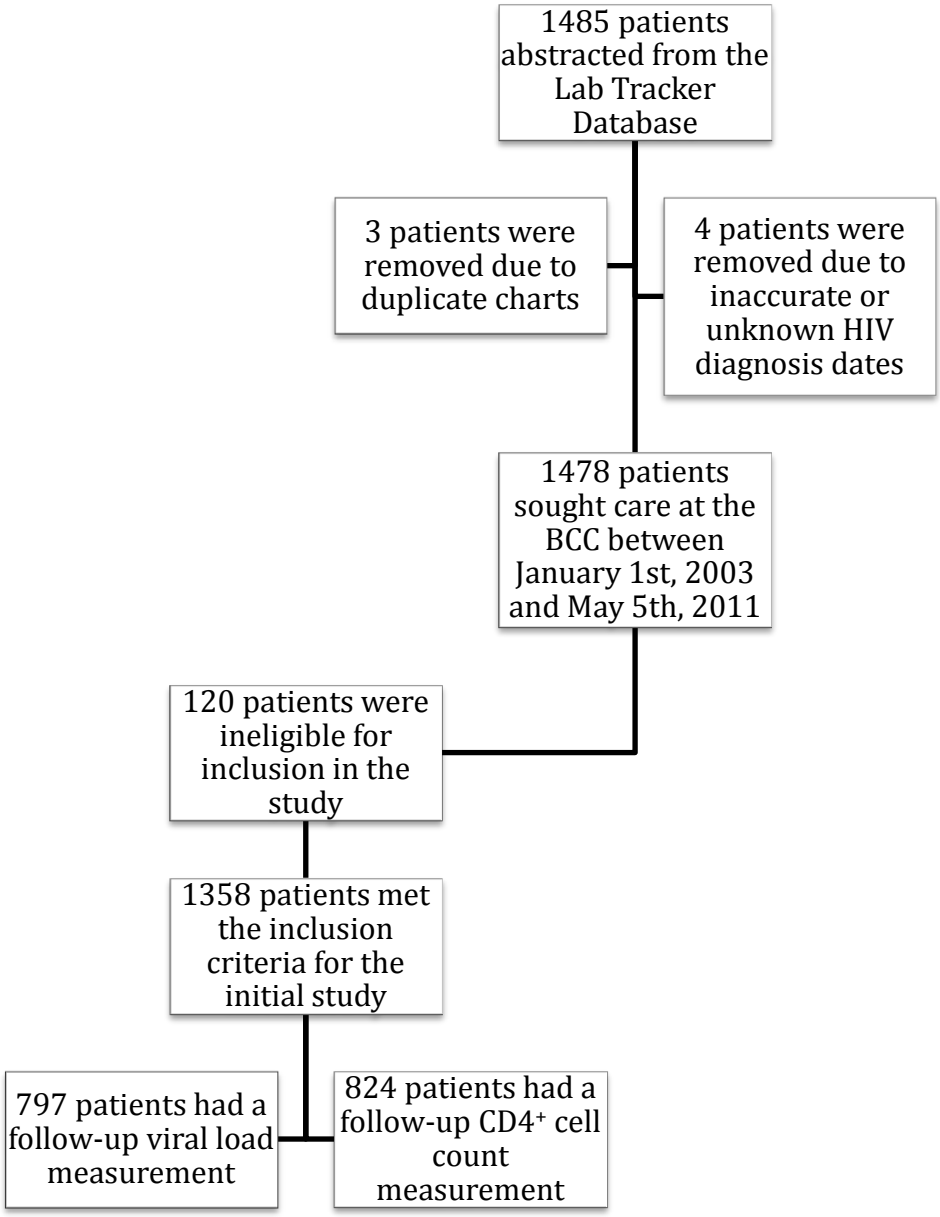

Figure 3.1 Flow chart of the Patients Enrolled in the Study

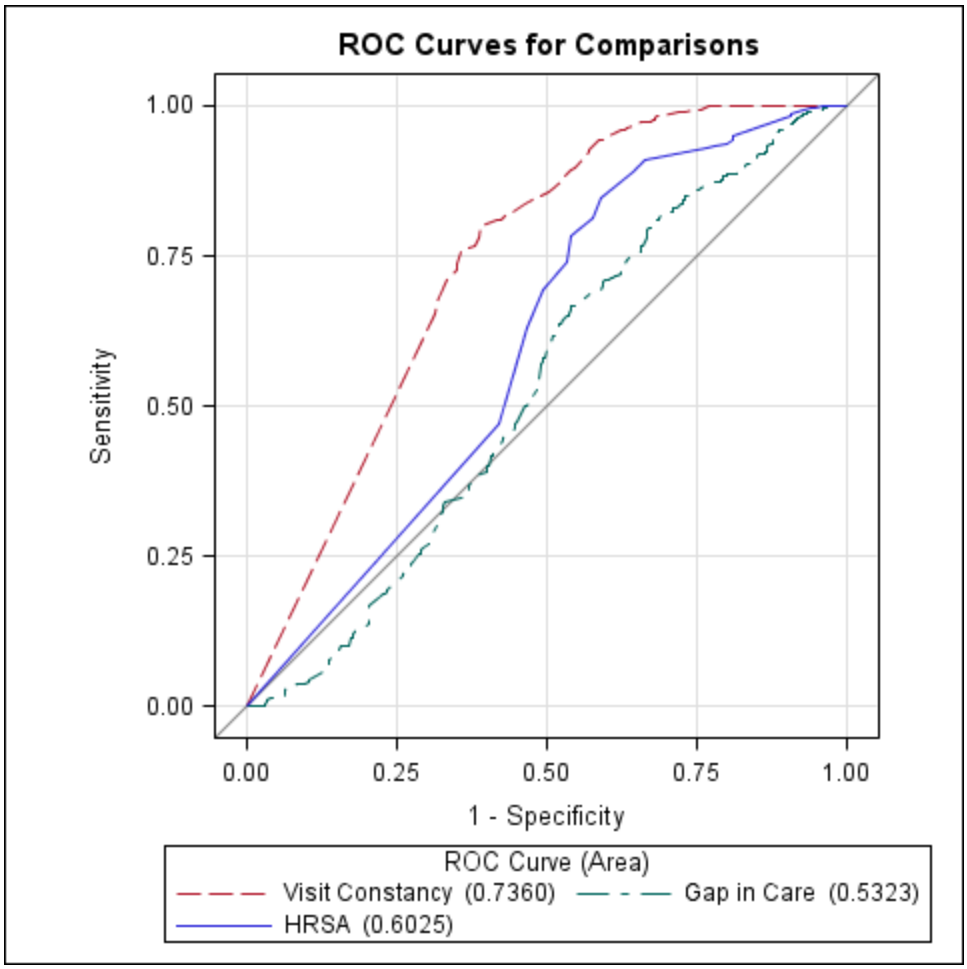

Figure 3.2 Receiver Operating Characteristic Curves Detecting Viral Suppression

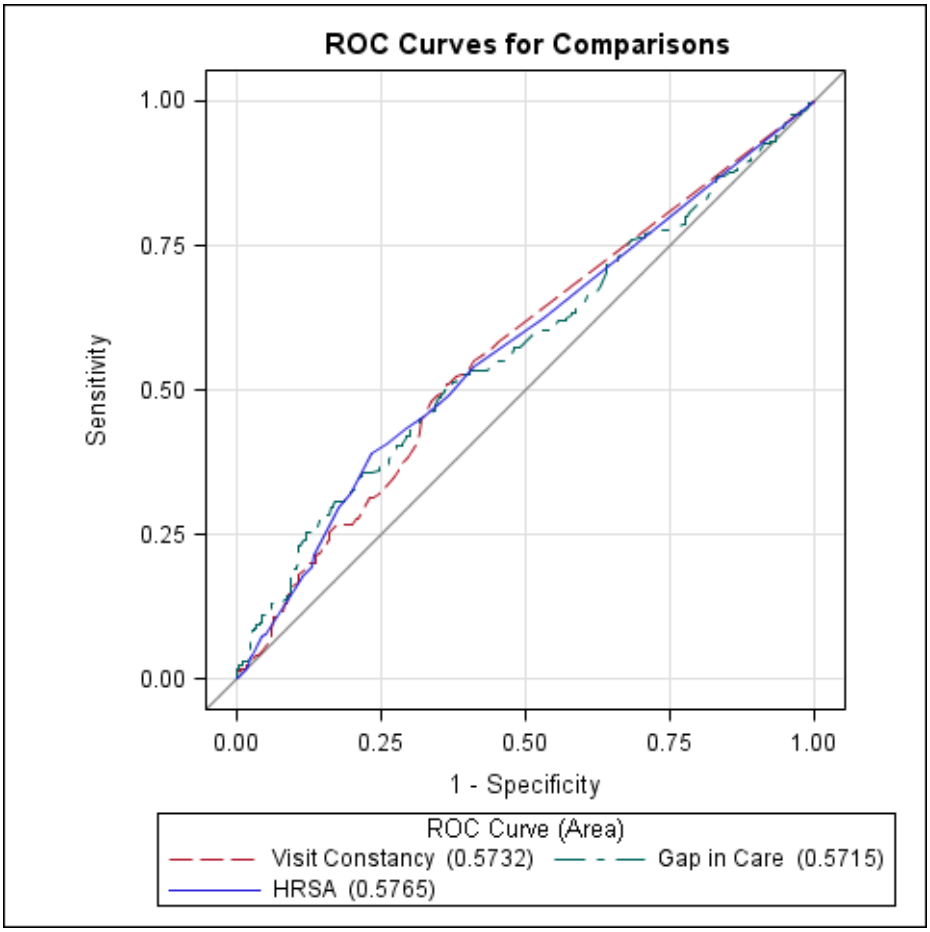

Figure 3.3 Receiver Operating Characteristic Curves Detecting CD4+ Cell Count Failure

Chapter Four

Impact of non-HIV Related Comorbidities on Retention in HIV Medical Care: Does Retention Improve over Time

Introduction

Despite the major advances and benefits of HIV medical care (i.e. HAART) and a publicly funded system which provides HIV medical care to those who otherwise would not seek care (Ryan White Modernization Act), a large portion of people living with HIV/AIDS (PLWHA) do not seek continuous medical care.[12] Approximately 40-50% of PLWHA's, who are aware of their HIV status, are not seeking optimal medical care, which can pose significant harms to the management of their HIV infection.[11-13] According to the national HIV/AIDS strategy for the United States, the goal is to increase the proportion of newly diagnosed patients linked to clinical care within three months of their diagnosis from 65% to 85%, and to increase the percentage of those clients enrolled in the Ryan White HIV/AIDS Program who are optimally retained in medical care from 73% to 80%, by 2015.[59]

It is imperative for PLWHA to maintain optimal care throughout the course of their infection, as PLWHA who are poorly retained in HIV medical care are less likely to receive the appropriate medications (e.g. HAART and Opportunistic Infections prophylaxis), are more likely to have poor medication adherence, and are more likely to acquire resistance to HAART.[15,19,34,85] Also, poorly retained HIV infected patients have difficulties maintaining viral load suppression as well as maintaining high $CD4^+$ cell counts.[21,24,25,28,44,45,48] Understanding the factors that impact retention to HIV medical care is important as researchers and clinicians feel that this should take priority over medication adherence.[73]

In recent years, researchers have established predictors of poor and optimal retention, but have focused solely on general socio-demographic factors (e.g. age, race, sex, and income) and how they predict poor retention for a specific time period.[21,38,40,43,46,60] Little is known about how retention changes over an extended time period and what factors may affect this change. For example, non-HIV related comorbidities like cancer, cardiovascular disease, respiratory disease, and mental health may have an impact on retention in medical care,[22,62,86,87] for there has been an increase in the number of comorbidities diagnosed among PLWHA (e.g. approximately 50% of PLWHA have a mental illness and 13% have both a mental illness and substance abuse).[59] Braithwaite et al conducted a mathematical model to show that the number of PLWHA with non-HIV related comorbidities will increase over time and that these conditions will probably be the cause of death in patients, not the underlying HIV infection.[88]

Researchers studying comorbid conditions have specifically focused on the impact of mental health illnesses and substance abuse problems on retention to medical care and have very short follow-up periods.[62,70,86] Giordano et al. observed PLWHA with a comorbid condition for two years, and showed that PLWHA with any type of comorbid condition were less likely to be poor retainers compared to those without a comorbid condition.[22] As PLWHA age and continue the long-term use of HAART, the likelihood of having multiple comorbid conditions increases, and it is important to understand how the acquisitions of comorbid conditions affect retention over time.

The purpose of this study is to understand the predictors of less than optimal retention in HIV medical care and to understand how the presence of one or more comorbid conditions affects retention over time among a cohort seeking care at a Ryan White clinic in Kentucky. This study extends prior research by observing multiple comorbid conditions and incorporating a longer observational period (9 years).

Methods

Study Design

To determine the impact comorbid conditions have on HIV medical care retention, a retrospective cohort study employing a medical chart review was conducted at an academic infectious disease clinic at the University of Kentucky (KY). Patients who sought care between January 1st, 2003 and May 1st 2011 were considered eligible for this study, and were followed until December 31st, 2011. During the follow-up period, patients were followed until the end of the study period (December 31st, 2011), death, or move out of service region. The study was approved by the University of KY Institutional Review Board.

Study Site

Patients diagnosed with HIV and referred to the Bluegrass Care Clinic (BCC) for medical care were considered for inclusion in the study. The BCC is a multi-disciplinary HIV care clinic located in an urban area in KY. The BCC is the largest of four HIV care providers in a 63 county area in KY federally funded through the Ryan White HIV/AIDS Treatment and Modernization Act of 2006, and non-federal funds through the Commonwealth of KY.

The BCC provides expert medical care by physicians, nurses, pharmacists, and other clinicians trained to deal with the complex management of a variety of infectious diseases, including HIV and related conditions. The clinic enhances access to and retention in primary health care and provides support services for Kentuckians living with HIV disease.

Study Population and Eligibility

Data for this study were abstracted from the HIV Lab Tracker ™, an electronic database located at the BCC. The HIV Lab Tracker ™ is an advanced electronic database solution for managing patients living with HIV. The electronic database encompasses a comprehensive list of information for each patient, which includes demographics, laboratory, medication, and clinical data.

Patients were considered for the study if they were diagnosed with HIV before or during the study period and were 18 years of age or older at the time of the study. To obtain the patients that met the initial criteria, patients were queried in the database on the following criteria: 1) HIV diagnosis date (May 1st, 2011 and earlier) and 2) Age (≥ 18 years). The query resulted in 1,485 patients who were pulled from the database and were initially eligible for the research study. Patients were included in the study if they sought HIV medical care at the BCC during the specified time period, had at least two completed clinic visits (intake visit and subsequent clinic visit), had at least 6 months of follow-up time, and had the appropriate dates recorded (Clinic visits, HIV Diagnosis, AIDS diagnosis). Of the 1,485 patients pulled from the database, 1,358 (91%) patients were included for follow-up.

The patients included in the study were all followed at 6-month intervals from their initial start date to the end of the follow-up period. Patients, whose initial start date came before the beginning of the study period (January 1st 2003), were followed from their first completed clinic visit in the time frame. During each 6-month period, the following

information was observed: the number of completed clinic visits, diagnoses of new infections/diseases (e.g. AIDS, opportunistic infections, Hepatitis C, non-HIV related comorbidities), number of hospitalizations, and/or death.

Study Measures

Baseline and clinical characteristics were abstracted from the medical charts. Race was categorized into white and non-white. Mode of transmission was categorized as heterosexual contact, injection drug use (IDU), men who have sex with men (MSM) and other. Insurance status at baseline was categorized into no insurance, Medicaid, Medicare, and private. A history of illicit drug use included individuals that reported use of cocaine, meth, and/or marijuana. A concurrent HIV/AIDS diagnosis was defined as an AIDS diagnosis within 30 days of an HIV diagnosis. Because the VL at baseline was measured in copies/ml and was not normally distributed, the results were transformed into log copies/ml. Death was obtained from the medical charts as well as the social security death index. For this index, each name and social security number were entered into a database to determine date of death.

For each patient in the study, the number of comorbid conditions diagnosed was observed every 6 months as well as the number of visits completed. A clinic visit was defined as an HIV medical outpatient care visit. Since laboratory tests were ordered by the HIV care physicians during every clinic visit, VL and $CD4^+$ cell count measurements were used as surrogate clinic visits. The non-HIV related comorbidities were defined as the seven most commonly diagnosed conditions at baseline among the patients in the study (Table 4.1). The comorbidities used in the analysis included renal disease, cancer (non-AIDS defining), cardiovascular (hypertension, heart disease, and coronary artery disease), cerebrovascular (stroke), respiratory (chronic obstructive pulmonary disease (COPD) and

asthma), diabetes, and mental health (depression). AIDS defining illnesses (ADIs) were observed at baseline and during each six month interval. The ADIs were defined using the 1993 revised classification system for HIV infection (Table 4.1).[77] Another condition collected was the diagnosis of Hepatitis C virus. All conditions were abstracted through the medical charts. Non-HIV related comorbidities and ADIS were treated as dichotomous variables (presence of any comorbidity/ADIs) and as continuous variables (the total number of comorbidities/ADIs diagnosed at each 6 month interval). The conditions were observed as continuous variables to determine how retention changes over time as the number of comorbid conditions increases.

Outcome Measures

Retention in care was the primary outcome in this study; it was defined as having at least one HIV medical outpatient visit within each 6-month interval (visit constancy) (yes/no). Visits completed were observed until the end of the study period, death, or lost to follow-up. The proportion of 6-month intervals with at least one visit was calculated for each patient; patients were divided into four groups based on the percentage of 6-month intervals with at least one visit. The groups were optimal retainers (100%), suboptimal retainers (99% - 75%), sporadic retainers (74% - 50%) and poor retainers (<50%). [21]

Statistical Analysis

Data were analyzed using SAS version 9.3 (Cary, NC). Descriptive statistics were calculated to describe the study population with means and standard deviations calculated for all continuous variables and frequencies and percentages calculated for all categorical variables. For the bivariate analysis, ANOVAs and chi-square tests of independence were employed to determine differences in retention groups for continuous and categorical variables, respectively.

The proportional odds assumption was assessed using the score test to determine whether the odds ratios can be interpreted as constant across the retention in care cut points and a proportional odds model could be employed.[80] Since the assumption was not valid, a multinomial logistic regression was used comparing different levels of retention to a base level (optimal retention). The multinomial regression analysis was employed to determine if comorbid conditions and other factors were associated with suboptimal, sporadic, and poor retention compared to optimal retention. Variables with p-values ≤0.15 in the bivariate analysis and confounding variables (based on previous literature) were included in the original model. Variables that did not appear to have an effect on the outcome or comorbid conditions were removed from the model. Akaike information criteria (AIC) were used to determine which model to use and Hosmer and Lemeshow goodness of fit test was produced to determine the fit of the model. In order to determine how the number of comorbidities diagnosed predicts retention, ADIs and non-HIV related comorbidities were observed as the sum of conditions diagnosed in the first multinomial regression. In the second multinomial regression model, each comorbid condition was included separately to determine the association between each specific condition while controlling for the other variables included in the model.

A generalized linear mixed model (GLMM) was used to determine the predictors that affect retention over time, in particular, the presence of one or more comorbid conditions. GLMMs have been used in research as an alternative way to fit a longitudinal model to non-normal data.[80,89] In this study, the dependent variable of interest was retention to care (yes/no). A GLMM was chosen for the analysis of this study as it has the flexibility to specify random effects and also generate subject-specific parameter estimates.[80,89] Fixed effects (i.e. age, race, sex, health insurance, and Hepatitis C) and random effects were included in the model. Random variation between patients was accounted for

using random intercepts. In order to obtain a likelihood function for the observed data, the random effects have to be integrated out. The integral approximation method allows for the approximation of the log likelihood, which allows for likelihood ratio tests to be performed among nested models and computation of likelihood-based fit statistics. The integral approximation was performed using the Gauss-Hermite Quadrature method. The covariance structure employed for this model was the variance component as it models a different variance component for each random effect.

The random-intercept model estimates the probability of being retained over time; variables with a *p*-value ≤0.15 in the bivariate analysis were initially included in this model. Two GLMMs were performed for this analysis. The first model included each of the seven comorbid conditions while controlling for the other variables. The second model included the number of comorbidities diagnosed as a continuous variable, which observed the sum of the number of conditions diagnosed during each patient-care interval. Age, number of comorbidities diagnosed, and number of ADIS diagnosed were included in the models as time-varying variables. AICs and likelihood ratio tests were used to determine which model was the best model and *p*-values <0.05 were regarded as statistically significant. Each model controlled for race, age, history of tobacco use, insurance type, history of Hepatitis C, and history of illicit drug use.

Results

Demographic and Clinical Characteristics of the Study Population

For the entire sample, the mean age at initiation was 38.2 ± 10.1 years, 81.2% were men, 70% were white, and the majority of the patients had MSM as their transmission category (57%). Approximately 49% lived below the federal poverty level and 27% had a history of illicit drug use (Table 4.2).

The majority of the patients entered the study with no insurance (42.6%) and only 25.8% had private insurance. Over half (53.3%) of the sample acquired AIDS during the study period, with 25% entering care with a concurrent HIV/AIDS diagnosis, and approximately 13% had a hepatitis c diagnosis. The majority of the sample was prescribed HAART during the course of the study period (84.5%) (Table 4.2).

Comorbidities and other Factors Associated with Rates of Retention

The average follow-up time for the study population was 5.75 ± 2.65 years (median = 6.20) years and the average number of completed visits during the 9-year study period was 39.6 ± 39.8 clinic visits (median = 28.0) (data not shown). Of the 1,358 Patients who were seeking HIV medical care at the BCC during the specified time period, only 48.6% were optimal retainers, while 19.1% were poor retainers (Table 4.2). In the bivariate analysis, optimal retainers were more likely white compared to non-whites (50.7% versus 43.3%, $p<0.0001$), living above the poverty level compared to those below the poverty level (59.6% versus 43.1%, $p<0.0001$), non-smokers compared to smokers (54.3% versus 43.0%, $p = 0.0003$), and those with private insurance compared to those with no insurance or Medicaid (53.2% versus 46.4%, 41.5%, respectively, $p=0.004$) (Table 4.2).

During the study period, 882 non-HIV related comorbidities were diagnosed in 610 (44.9%) patients, with approximately 31% of those having two or more comorbidities diagnosed. Of the 610 patients that had a comorbidity condition diagnosed, 11% had a comorbidity condition only at baseline and approximately 34% were diagnosed with a comorbidity condition during the study period. Depression (430 diagnoses) was the most prevalent comorbidity, followed by respiratory disease (110), diabetes (92), and cardiovascular disease (76) (Table 4.3).

The bivariate analysis suggested that patients with non-HIV related comorbidities were more likely to be optimal retainers compared to those without these comorbidities (55.1% versus 43.2%, p <0.0001). Patients with cancer, cardiovascular, diabetes, or mental health disorders were more likely to be optimal retainers compared to their counterparts (Table 4.3).The non-HIV related comorbidities were divided into three groups (none, one, and two+) and figure 4.1 shows that those patients with two or more comorbidities were more likely to be optimal retainers compared to those with one or no comorbidity (65.5% versus 50.6% and 43.3%, respectively, p <0.0001), and patients with no comorbidity were more likely to be poor retainers compared to those with one or two or more comorbidities (25.0% versus 14.5% and 5.8%, respectively, p<0.0001) (Figure 4.1). This suggests a dose-response relationship between the number of comorbid conditions diagnosed and optimal and poor retention.

Table 4.4 presents the multinomial logistic regression results for factors predicting retention to care categories. Compared to optimal retention, suboptimal retainers were at an increased odds among the ≤24 year age group (OR = 2.23; 95% CI = 1.21-4.11), 25-34 year age group (OR = 2.38; 95% CI = 1.55-3.67), and 35-44 year age group (OR = 1.52; 95% CI =1.03-2.24) compared to the >44 year age group. The odds of suboptimal retention, compared to optimal retention, was significantly higher among heterosexuals (OR = 1.68; 95% CI = 1.09-2.60) compared to MSM, those living below the poverty level (OR = 1.92; 95% CI = 1.32-2.79) compared to those above the poverty level, patients with a history of smoking (OR = 1.54; 95% CI = 1.13-2.09) compared to those who were smoke free, and those with an AIDS diagnosis (OR = 1.75; 95% CI = 1.18-2.59). Suboptimal retention was significantly less likely among females (OR = 0.56; 95% CI = 0.34-0.91) compared to males.

Sporadic retention, compared to optimal retention, had significantly higher odds among those aged 25-34 years (OR = 2.21; 95% CI = 1.30-3.75) compared to those aged >44 years, those living below the federal poverty level (OR = 2.26; 95% CI = 1.40-3.67), and those with a history of Hepatitis C (OR = 1.91; 95% CI =1.10 – 3.30). Poor retention, compared to optimal retention, was at significantly higher odds among non-whites (OR = 1.80; 95% CI = 1.23-2.63) compared to whites, younger individuals, tobacco users (OR = 1.57; 95% CI = 1.10-2.23), non-insurers (OR = 1.67; 95% CI = 1.04-2.70) and Medicaid (OR = 2.21; 95% CI = 1.21-4.02) compared to private insurers, and those with $CD4^+$cell counts <200 (OR = 2.29; 95% CI = 1.29-4.08) compared to those with $CD4^+$ cell counts >350 at baseline (Table 4.4).

The results of the multinomial regression show that having one or more non-HIV related comorbidity was predictive of retention to HIV medical care. For suboptimal, sporadic, and poor retention, the odds of having any of the studied comorbidities decreased by 0.82 (95% CI = 0.69-0.99), 0.73 (95% CI = 0.56-0.94), and 0.63 (95% CI = 0.48-0.81), respectively compared to optimal retention (Table 4.4). This data indicated that patients having any of the studied comorbidities had an increased chance of being in optimal care. Observing the non-HIV related comorbidities separately in the multinomial model (Figures 4.2 – 4.4); sporadic retainers, compared to optimal retainers, were at lower odds among those patients diagnosed with diabetes (OR = 0.31; 95% CI = 0.11-0.91) (Figure 4.2). Compared to optimal retainers, poor retainers were at lower odds among those individuals diagnosed with diabetes (OR = 0.32; 95% CI = 0.10-0.98) and depression (OR = 0.61; 95% CI = 0.40-0.93) (Figure 4.3). Although not significant, compared to optimal retainers, suboptimal, sporadic, and poor retainers were at increased odds among those with a respiratory comorbid condition (Figures 4.2 – 4.4).

Factors Associated with Retention over Time

The median number of 6-month periods observed for each individual was 11.0 (IQR: 5, 16). Figure 4.5 shows the percentage of individuals who retained (at least one visit) in each 6-month interval. At the start of the study, there was 100% retention among the individuals seeking care, but as time progressed, the percent of individuals retained in care decreased. Over the course of the study period, the percentage of patients retained in care was higher among those with at least one non-HIV related comorbid condition compared to those without a comorbid condition (Figure 4.6). Overall the average percentage of 6-month intervals with at least one visit among the entire cohort was 77.6 ±29.9% (median = 94.1). The average percentage of 6-month intervals with at least one visit was higher for those individuals with two or more comorbid conditions (88.8 ±21.7%) compared to those with one condition (82.1 ±25.7%) or none (72.5 ±32.6%) ($p<0.0001$) (Figure 4.7).

Figure 4.8 presents the percentage of individuals who retained through each interval categorized by when a comorbid condition was diagnosed. Patients with a comorbid condition diagnosed at baseline and another condition diagnosed during the study period were more likely to be retained in care compared to the other groups. The figure also shows that while all four groups had a decrease in the percent retained in the early stages of the follow-up period, those with both a baseline and study comorbid condition had slight increases in the percent retained. Figure 4.9 presents the percent retained for each comorbid condition separately. Patients with cancer, renal disease, diabetes, and cerebrovascular conditions appeared to have increased retention throughout the study period.

The GLMMs estimated how non-HIV related comorbidities were associated with retention over time. Table 4.5 presents the associations between each comorbid condition and retention over time. Controlling for all variables included in the model, a patient diagnosed with depression during the study period, were at an increased odds of optimal retention over time (OR = 3.80; 95% CI = 2.54 – 5.68). Individuals with diagnosed diabetes during the study period had 5.71 (95% CI = 2.49 – 13.16) times the odds of improved retention compared to those without diabetes. A patient diagnosed with cancer or a cardiovascular condition had 3.89 (95% CI = 1.54 – 9.80) and 3.16 (95% CI = 1.33-7.52) times the odds, respectively of improved retention over time compared to one without cancer or a cardiovascular condition.

Table 4.6 presents the GLMM which includes, the number of non-HIV related comorbidities as a time-varying covariate. As the number of non-HIV related comorbid conditions diagnosed increased during the study, the odds of retention increased (OR = 2.28; 95% CI = 1.83-2.71), while controlling for the other variables in the model. As the number of ADIs diagnosed during the study increased for an individual, the odds of retention over time increased (OR = 1.84; 95% CI = 1.45 – 2.27). Throughout the follow-up period, non-whites compared to whites had a difficult time retaining in care as these individual were at decreased odds of retaining over time (OR = 0.36; 95% CI = 0.24-0.55). While controlling for the other variables included in the model, individuals without insurance or Medicaid were 0.45 (95% CI = 0.28-0.72) and 0.30 (95% CI = 0.17-0.55) times the odds, respectively of retaining in care over time. Lastly, having a Hepatitis C diagnosis meant worse retention over time compared to those without a Hepatitis C diagnosis (OR = 0.51; 95% CI = 0.29-0.89).

Discussion

Retention in HIV medical care was observed among an HIV population seeking care at a Ryan White funded clinic. The purpose of this study was to determine the predictors of retention and to shed light on the impact comorbidities have on retention to care over time. This study is one of the few studies to focus specifically on a Ryan White population as well as observe a time period longer than 1 to 2 years. Of the 1,358 individuals who were included in the study, only 48.6% had optimal retention (a visit in every 6-month interval). This statistic is significantly below the national average as it is suggested that approximately 73% of clients enrolled in Ryan White funded clinics and 60% of patients enrolled in other medical clinics are consistently retained in HIV medical care[13,59].

With the multinomial logistic regression, we were able to determine what factors predicted suboptimal, sporadic, or poor retention compared to optimal retention. We found that age at baseline, non-whites, heterosexual transmission, low income, tobacco use, Hepatitis C, and lower $CD4^+$ cell counts were predictive of patients being in at least one less than optimal group of retention. Controlling for socioeconomic status, race, insurance status, disease severity, and younger age were strongly predictive of all three retention groups. Individuals who were aged 25-34 years were almost 4 times the odds of being poor retainers compared to those aged >44 years. This finding agrees with other studies as researchers have shown that older PLWHA's are more likely to retain in care compared to younger individuals [19,22,28]. It is important to focus on the younger HIV population as this age group makes up the majority of individuals diagnosed and living with HIV.[72,90-92] Retention interventions should be set in place that target the younger HIV population as this may increase retention and reduce the risk of transmission.

The finding that blacks and Hispanics were at greater odds of poor retention, even after controlling for socioeconomic status (income and insurance) and other variables, is discouraging. Multiple studies have suggested that blacks and Hispanics have significant difficulty retaining in HIV medical care compared to whites. [16,21,22,25,28,29,32,33,93] The BCC provides assistance to those individuals who may be of low economic status by providing programs such as the AIDS drug and assistance programs. Unfortunately, this study did not consider potential barriers to retention like transportation, social stigma related to HIV/AIDs, or distrust of the medical system, as this has been shown to be a major factor for poor retainers, especially among minorities.[63,64] Further research needs to be done to understand the factors that contribute to blacks and Hispanics having poor retention. This disparity in care may be a major reason why blacks and Hispanics living with HIV/AIDS have worse HIV outcomes compared to whites. [22,25]

Although individuals seeking HIV medical care at a Ryan White funded clinic are provided opportunities and assistance to maintain the management of their HIV infection at little to no costs, socioeconomic status was significantly predictive of suboptimal to poor retention. Individuals living below the federal poverty line were more likely to be suboptimal and sporadic retainers and those with no insurance or only Medicaid had greater odds of being poor retainers compared to their counterparts. This is interesting as these individuals are missing their opportunities to reduce their risk of disease progression. The costs of treatment were not considered in this study, but a few possibilities may explain this result. Individuals of low socioeconomic status may not have optimal retention due to lack of transportation, 'leave' time for work, or child care services.[63,64,66] Transportation may be a key factor to poor retention as a majority of the patients that seek care are from rural areas in KY. It is pertinent to understand the barriers that prevent patients from retaining in care and to develop interventions which will engage patients into care.

It is estimated that approximately 50% of PLWHA have comorbidities such as cancer, heart disease, mental health, and renal disease, and that substance abuse and alcoholism are also highly prevalent among PLWHAs.[59] Approximately 45% of the individuals in this study had a least one non-HIV related comorbidity. Of the six comorbidities included in the analysis, depression was the most prevalent, followed by respiratory, diabetes, and cardiovascular. The results of the study suggest that having one or more comorbidity actually facilitates retention in care. Individuals with at least one comorbid condition were more likely to be optimal retainers compared to those individuals who were 'healthier.' Approximately 31% of those with comorbid conditions had two or more conditions diagnosed during the study period. The multinomial regression suggest that as the number of comorbid conditions increased, the less likely they were to be suboptimal, sporadic, or poor retainers. This finding mirrors the findings of Giordano et al., which showed that individuals with comorbid conditions were more likely to retain in care.[22]

Fleming et al showed that individuals living with multiple morbid conditions were more likely to seek colorectal screening compared to those with no condition diagnosed.[94] Although Fleming et al's study focused on cancer screening, their results are similar to ours which shows that these individuals are more likely to seek proper care and prevention measures, perhaps because they have multiple chronic conditions to worry about. Our interpretation of these studies is that individuals with comorbid conditions are already seeking care providing the opportunity for physicians to emphasize the importance of being retained in care to manage their medical conditions.

Individuals with diabetes and mental health disorders diagnosed during the study period had higher odds of optimal retention. This finding contradicts some researcher's findings as they suggest that individuals with mental health disorders like depression have greater difficulty retaining in HIV care.[62] We did, however, find that individuals diagnosed with depression prior to initiation of HIV medical care (baseline) were less likely to be optimal retainers compared to those who were diagnosed during the study period. Individuals who are diagnosed with HIV and have a prior mental illness may need to be referred to mental health services immediately as this may help promote and increase retention in care. Researchers have shown than individuals that take part in ancillary services like mental health services, are more likely to optimally retain in care.[53-55,67,70] A marginally significant result was that those individuals with respiratory illnesses (Asthma and COPD) had greater odds of sporadic and poor retention. This finding should be examined further regarding why these individuals are failing to retain HIV/AIDS care. To our knowledge, this is the first study to observe comorbid conditions separately regarding the impact on retention in care.

The GLMM was performed to understand how retention changes over time for this Ryan White population. The results showed that over time, as the number of comorbid conditions diagnosed increased the more likely an individual was to retain in care. Having multiple ADIs diagnosed during the study period was also predictive of improved retention. Observing each comorbid condition separately, it was shown that individuals with diabetes, cancer, cardiovascular, and depression conditions had much greater odds of retention compared to those without those conditions. This implies that individuals who are 'healthier' are not consistently engaged in care. One could argue that PLWHA who feel 'healthy' find it unnecessary to seek care, whereas those who are sicker feel the need to engage in care more frequently. Some research supports an alternative hypothesis that the

healthy (not the sick) seek care more frequently, maintaining their 'healthy' status.[50] Further research should be conducted on this 'healthy' population to determine how poor retention affects specific short and long-term HIV outcomes like viral load suppression, progression to AIDS, or death.

It is difficult for individuals with a history of Hepatitis C to be retained in care. Retention to HIV medical care worsens over time for individuals co-infected with Hepatitis C. Some also argue that individuals with substance abuse problems are less likely to retain in care, perhaps because there is a strong correlation between substance abusers and Hepatitis C among PLWHA.[59] Nonetheless, in our study, there was no significant interaction between individuals using illicit drugs and Hepatitis C, although those with Hepatitis C did have difficulties maintaining retention.

We showed a decreased retention over time among those who did not have any comorbidity. In order for the clinical management of HIV to be successful it is critical for individuals to remain engaged in care. It was shown in chapter 3 that approximately 16% of the sample had gaps in care that were >12 months. Re-engaging these individuals that fall out of care should be a major priority among clinicians and public health researchers. Multiple strategies and interventions should be developed that seek out these individuals and reintegrate them to HIV care. To our knowledge there has not been any study to definitively show the best strategy in reengaging these individuals.

This study has both strengths and limitations. For example, the chart review was only able to assess whether patients had been diagnosed with comorbid conditions but not the severity of these conditions; thus we were unable to determine the significance or magnitude of any relationship between comorbidity severity condition and retention to care. We also did not observe ancillary services such as mental health programs,

transportation services, and case managers. The services could confound the relationship between retention in care over time and comorbid conditions. The Ryan White population enrolled in this study may not be generalizable to other PLWHA that are not enrolled in Ryan White programs, so these results should be interpreted and compared with caution. Since our definition of a clinic visit includes only visits from HIV care providers, retention in care may be underestimated for this study population. Although this may be so, the definition is consistent with other studies which defined retention in HIV medical care.[14] On a related note, individuals were excluded from the study if they did not have at least two or more clinic visits completed during the specified time period. This exclusion could lead to an underestimation of poor retainers. The number excluded due to this criterion was small, and there were no significant differences between the cohorts.

The major strengths of our study are the relatively large sample size, compared to other studies that investigate retention in care and the lengthy follow-up period (9years) compared to most other studies of shorter duration (1-3 years).[13,22]

Conclusion

The current study showed that younger age, non-whites, no insurance, and those with a history of AIDS were more likely to have poor retention, while individuals with non-HIV related comorbidities were less likely to have poor retention. It was suggested that over time, retention in care decreases slightly among this Ryan White population. Over time, patients with comorbid conditions had improved retention in HIV medical care.

Having multiple ADIs diagnosed during the study period was also predictive of improved retention. Not retaining in HIV care can pose significant problems for these individuals as it can possibly lead to medication resistance, progression to AIDS or even death. More research needs to be done to identify factors that improve retention over time and to quantify the relative impact of these factors.

Table 4.1. List of conditions observed among those seeking HIV medical care at the BCC: 2003-2011

Condition	Condition
AIDS-defining Illnesses/Conditions	**Non-HIV related comorbidities**
Candidiasis, pulmonary	Renal Disease
Candidiasis, esophageal	Cardiovascular
Cervical Cancer, invasive	Cerebrovascular
	Respiratory
Coccidioidomycosis	Diabetes
Cytomegalovirus	Cancer
Encephalopathy	Mental Health (Depression)
Herpes Simplex Virus (HSV)	
Histoplasmosis	**Other**
Kaposis Sarcoma	Hepatitis C
Lymphoma, Burkitt's	
Mycobacterium avium complex (MAC)	**Behavioral**
Mycobacterium tuberculosis (TB)	History of Tobacco Smoke
Pneumocystis carinii pneumonia (PCP)	History of Illicit Drug Use (Marijuana, Cocaine, and Crystal Meth)
Progressive Multifocal Leukoencephalopathy (PML)	
Toxoplasmosis	
Wasting Syndrome	

Table 4.2. Socio-demographic and Clinical Characteristics Among Adults Diagnosed and Living with HIV/AIDS by the Proportion of 6 month intervals with at Least One Clinic Visit : 2003 - 2011

	Total	Optimal Retention n (%)	Suboptimal Retention n (%)	Sporadic Retention n (%)	Poor Retention n (%)	p
Total	1358	660 (48.6)	281 (20.7)	158 (11.6)	259 (19.1)	
Sex						
Female	256 (18.9)	128 (50.0)	48 (18.8)	33 (12.9)	47 (18.4)	0.8
Male	1102 (81.2)	532 (48.3)	233 (21.1)	125 (11.3)	212 (19.2)	
Race						
Non-White	404 (29.8)	175 (43.3)	69 (17.1)	54 (13.4)	106 (26.2)	<0.001
White	952 (70.2)	483 (50.7)	212 (22.3)	104 (10.9)	153 (16.1)	
Age at Baseline						
≤24 yrs	136 (10.0)	56 (41.2)	28 (20.6)	21 (15.4)	31 (22.8)	<0.001
25 - 34 yrs	362 (26.7)	143 (39.5)	86 (23.8)	48 (13.3)	85 (23.5)	
35 - 44 yrs	504 (37.1)	245 (48.6)	108 (21.4)	53 (10.5)	98 (19.4)	
>44 yrs	356 (26.2)	216 (60.7)	59 (16.6)	36 (10.1)	45 (12.6)	
Age mean years (std)	38.2 (10.1)	39.7 (10.2)	36.9 (9.7)	37.2 (10.5)	36.4 (9.3)	<0.001
Mode of Transmission						
Heterosexual	385 (28.4)	178 (46.2)	79 (20.5)	44 (11.4)	84 (21.8)	0.06
IDU	122 (9.0)	55 (45.1)	22 (18.0)	20 (16.4)	25 (20.5)	
Other	72 (5.3)	26 (36.1)	23 (31.9)	11 (15.3)	12 (16.7)	
MSM	777 (57.3)	401 (51.6)	157 (20.2)	82 (10.6)	137 (17.6)	
Employment Status						
Employed	501 (45.8)	276 (55.1)	113 (22.6)	51 (10.2)	61 (12.2)	0.07
Unemployed	402 (36.0)	192 (47.8)	91 (22.6)	46 (11.4)	73 (18.2)	
Other	215 (19.2)	123 (57.2)	41 (19.1)	26 (12.1)	25 (11.6)	
Income[a]						
≤10,000	662 (48.8)	285 (43.1)	166 (25.1)	97 (14.7)	114 (17.2)	<0.001
>10,000	446 (32.8)	266 (59.6)	91 (20.4)	36 (8.1)	53 (11.9)	
History of Tobacco Use						
Yes	686 (50.5)	295 (43.0)	163 (23.8)	90 (13.1)	138 (20.1)	<0.001
No	672 (49.5)	365 (54.3)	118 (17.6)	68 (10.1)	121 (18.0)	
History of Illicit Drug Use						
Yes	365 (26.9)	160 (43.8)	88 (24.1)	55 (15.1)	62 (17.0)	0.01
No	993 (73.1)	500 (50.4)	193 (19.4)	103 (10.4)	197 (19.8)	

Table 4.2. Continued

	Total	Optimal Retention n (%)	Suboptimal Retention n (%)	Sporadic Retention n (%)	Poor Retention n (%)	p
Insurance Type						
No Insurance	569 (42.6)	264 (46.4)	111 (19.5)	71 (12.5)	123 (21.6)	0.004
Medicaid	212 (15.9)	88 (41.5)	49 (23.1)	27 (12.7)	48 (22.6)	
Medicare	211 (15.8)	120 (56.9)	41 (19.4)	22 (10.4)	28 (13.3)	
Private	344 (25.8)	183 (53.2)	80 (23.3)	37 (10.8)	44 (12.8)	
Concurrent Diagnosis						
Concurrent	341 (25.1)	15 (54.3)	73 (21.4)	37 (10.9)	46 (13.5)	0.01
Non-Concurrent	1017 (74.9)	475 (46.7)	208 (20.5)	121 (11.9)	213 (20.9)	
History of AIDS Diagnosis						
Yes	724 (53.3)	354(48.9)	176 (24.3)	79 (10.9)	115 (15.9)	<0.001
No	634 (46.7)	306 (48.3)	105 (16.6)	79 (12.5)	144 (22.7)	
History of Hospitalizations						
Yes	738 (54.3)	403 (54.6)	158 (21.4)	84 (11.4)	93 (12.6)	<0.001
No	620 (45.7)	257 (41.5)	123 (19.8)	74 (11.9)	166 (26.8)	
Hepatitis C						
Yes	172 (12.7)	67 (39.0)	38 (22.1)	31 (18.0)	36 (20.9)	0.01
No	1186 (87.3)	593 (50.0)	243 (20.5)	127 (10.7)	223 (18.8)	
HAART Use						
Yes	1148 (84.5)	589 (51.3)	264 (23.0)	125 (10.9)	170 (14.8)	<0.001
No	210 (15.5)	71 (33.8)	17 (8.1)	33 (15.7)	89 (42.4)	
CD4+ Cell Counts[a]						
<200	390 (28.7)	188 (48.2)	80 (20.5)	41 (10.5)	81 (20.8)	<0.001
200 - 350	150 (11.1)	82 (54.7)	33 (22.0)	19 (12.7)	16 (10.7)	
>350	458 (33.7)	237 (51.8)	124 (27.1)	48 (10.5)	49 (10.7)	
Initial Viral Load mean log copies (std)	6.75 (3.05)	6.9 (3.2)	6.6 (3.0)	6.3 (2.9)	6.7 (2.9)	0.19

[a]Individuals with missing information were included in the calculation of percentages

Note: P values obtained using ANOVA and chi-square tests of independence for continuous and categorical variables, respectively

Table 4.3. Presence of Non-HIV related Comorbidities among 1358 Individuals Diagnosed and Living with HIV/AIDS by the Proportion of 6 Month Intervals with at Least one Clinic Visit: 2003-2011

	Total	Optimal Retention n (%)	Suboptimal Retention n (%)	Sporadic Retention n (%)	Poor Retention n (%)	p
Any Comorbidity						
Yes	610 (44.9)	336 (55.1)	140 (23.0)	62 (10.2)	72 (11.8)	<0.001
No	748 (55.1)	324 (43.2)	141 (18.9)	96 (12.8)	187 (25.0)	
Comorbidity Types						
Renal						
Yes	28 (2.1)	17 (60.7)	7 (25.0)	1 (3.6)	3 (10.7)	0.29
No	1330 (97.9)	643 (48.4)	274 (20.6)	157 (11.8)	256 (19.3)	
Cancer						
Yes	65 (4.8)	43 (66.2)	10 (15.4)	4 (6.2)	8 (12.3)	0.03
No	1293 (95.2)	617 (47.7)	271 (21.0)	154 (11.9)	251 (19.4)	
Cardiovascular						
Yes	76 (5.6)	50 (65.8)	17 (22.4)	7 (9.2)	2 (2.6)	0.001
No	1282 (94.4)	610 (47.6)	264 (20.6)	151 (11.8)	257 (20.1)	
Cerebrovascular						
Yes	17 (1.3)	11 (64.7)	3 (17.7)	2 (11.8)	1 (5.9)	0.46
No	1341 (98.8)	649 (48.4)	278 (20.7)	156 (11.6)	258 (19.2)	
Respiratory[a]						
Yes	110 (8.1)	49 (44.6)	30 (27.3)	16 (14.6)	15 (13.6)	0.13
No	1248 (91.9)	611 (49.0)	251 (20.1)	142 (11.4)	244 (19.6)	
Diabetes						
Yes	92 (6.8)	62 (67.4)	20 (21.7)	4 (4.4)	6 (6.5)	<0.001
No	1266 (93.2)	598 (47.2)	261 (20.6)	154 (12.2)	253 (20.0)	
Mental Health[b]						
Yes	430 (31.7)	241 (56.1)	97 (22.6)	44 (10.2)	48 (11.2)	<0.001
No	928 (68.3)	419 (45.2)	184 (19.8)	114 (12.3)	211 (22.7)	

Note: P values obtained using chi square tests of independence

[a]Respiratory disease consists of individuals with diagnosed Asthma or COPD

[b]Mental Health includes Depression

Table 4.4. Multinomial Logistic Regression of the Predictors of Retention to Medical Care among 1358 Individuals Living with HIV/AIDS : 2003 - 2011

	Suboptimal retention vs. optimal retention		Sporadic retention vs. optimal retention		Poor retention vs. optimal retention	
Variable	aOR	95% CI	aOR	95% CI	aOR	95% CI
Sex						
Female vs. Male	**0.56**	**0.34-0.91**	0.79	0.44-1.40	0.6	0.35-1.03
Race						
Non-White vs. White	0.83	0.57-1.19	1.28	0.84-1.95	**1.8**	**1.23-2.63**
Age at Baseline						
≤24 vs. >44 years	**2.23**	**1.21-4.11**	**2.08**	**1.03-4.17**	**2.28**	**1.15-4.50**
25 - 34 vs. >44 years	**2.38**	**1.55-3.67**	**2.21**	**1.30-3.75**	**3.89**	**2.34-6.46**
35 - 44 vs. >44 years	**1.52**	**1.03-2.24**	1.3	0.80-2.14	**2.15**	**1.35-3.43**
Mode of Transmission						
Heterosexual vs. MSM	**1.68**	**1.09-2.60**	1.35	0.78-2.33	1.54	0.95-2.50
IDU vs. MSM	0.86	0.47-1.57	1.07	0.55-2.09	0.9	0.45-1.77
Other vs. MSM	**3.15**	**1.64-6.04**	1.89	0.84-4.24	1.1	0.49-2.48
Income						
≤10,000 vs. >10,000	**1.92**	**1.32-2.79**	**2.26**	**1.40-3.67**	1.48	0.95-2.30
History of Tobacco Use						
Yes vs. No	**1.54**	**1.13-2.09**	1.45	0.99-2.13	**1.57**	**1.10-2.23**
History of Illicit Drug Use						
Yes vs. No	1.24	0.88-1.76	1.89	0.82-1.91	0.73	0.48-1.11
Insurance Type						
No Insurance vs. Private	**0.64**	**0.42-0.97**	0.78	0.47-1.30	**1.67**	**1.04-2.70**
Medicaid vs. Private	0.76	0.45-1.31	0.9	0.47-1.73	**2.21**	**1.21-4.02**
Medicare vs. Private	**0.57**	**0.35-0.93**	0.79	0.41-1.49	1.21	0.65-2.24
AIDS Diagnosis						
Yes vs. No	**1.75**	**1.18-2.59**	1.23	0.74-2.04	0.94	0.57-1.53
CD4+ Cell Counts						
<200 vs. >350	**0.56**	**0.36-0.87**	0.96	0.53-1.74	**2.29**	**1.29-4.08**
200 – 350 vs. >350	**0.6**	**0.36-0.98**	1.05	0.56-1.99	1.13	0.57-1.99
History of Hospitalizations						
Yes vs. No	**0.68**	**0.49-0.93**	0.71	0.48-1.04	**0.39**	**0.26-0.56**
Hepatitis C						
Yes vs. No	1.38	0.84-2.24	**1.91**	**1.10-3.30**	1.29	0.74-2.25
AIDS Defining Illnesses	1.14	0.98-1.33	0.95	0.76-1.18	0.87	0.70-1.09
Non-HIV Related Comorbidity	**0.82**	**0.69 - 0.99**	**0.73**	**0.56-0.94**	**0.63**	**0.48-0.81**

Table 4.5. Generalized Linear Mixed Model to determine the Association between Comorbid Conditions and Retention over time among patients seeking care at the BCC: 2003-2011

Comorbid Condition	Total (%)	Unadjusted OR	95% CI	Adjusted OR	95% CI
Depression (yes vs. no)	430 (31.7)	**6.80**	**4.37-10.64**	**3.80**	**2.54-5.68**
Renal Disease (yes vs. no)	28 (2.1)	**5.00**	**1.04-23.81**	0.82	0.22-3.13
Cancer (yes vs. no)	65 (4.8)	**6.94**	**2.41-20.0**	**3.89**	**1.54-9.80**
Respiratory (yes vs. no)	110 (8.1)	1.87	0.88-3.94	1.15	0.61-2.18
Diabetes (yes vs. no)	92 (6.8)	**14.29**	**5.71-35.71**	**5.71**	**2.49-13.16**
Cardiovascular (yes vs. no)	76 (5.6)	**16.39**	**6.13-43.48**	**3.16**	**1.33-7.52**
Cerebrovascular (yes vs. no)	17 (1.3)	5.29	0.66-41.67	0.75	0.13-4.18

Note: The model controlled for race, age (in years), history of tobacco use, insurance type, hepatitis c, illicit drug use, prescription of HAART, and year of HIV

Table 4.6. Generalized Linear Mixed Model to determine Retention over time among patients seeking care at the BCC: 2003-2011

Variable	aOR	95% CI
Comorbidities	**2.28**	**1.83-2.71**
AIDS Defining Illnesses	**1.84**	**1.45-2.27**
Race (Non-White versus White)	**0.36**	**0.24 – 0.55**
Age (years)	**1.03**	**1.01-1.05**
Tobacco Use Yes vs. No	**0.65**	**0.45-0.96**
Insurance Type		
No Insurance vs. Private	**0.45**	**0.28-0.72**
Medicaid vs. Private	**0.30**	**0.17-0.55**
Medicare vs. Private	0.92	0.50-1.68
Hepatitis C Yes vs. No	**0.51**	**0.29-0.89**
Illicit Drug Use Yes vs. No	1.04	0.67-1.61

Note: The GLMM controlled for those initiating HAART and the year of HIV diagnosis.

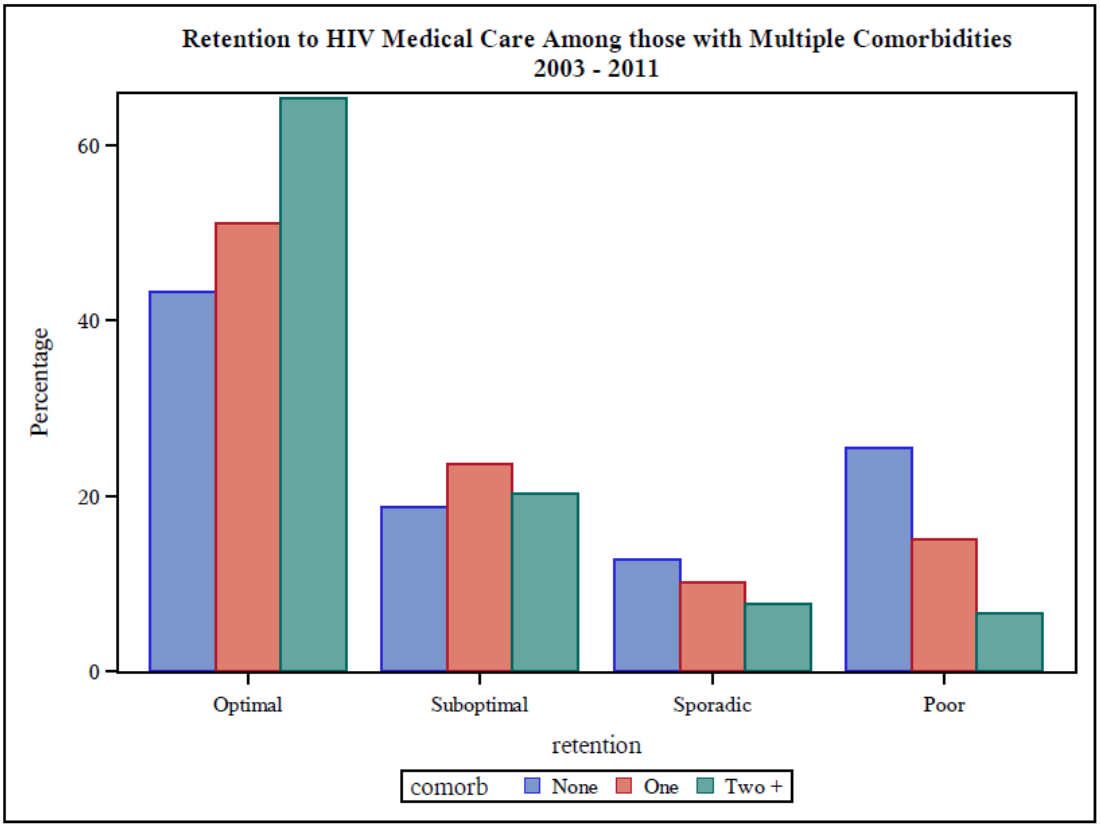

Figure 4.1 Status of Retention to HIV Medical Care among those with Multiple Non-HIV Related Comorbidities: 2003-2011

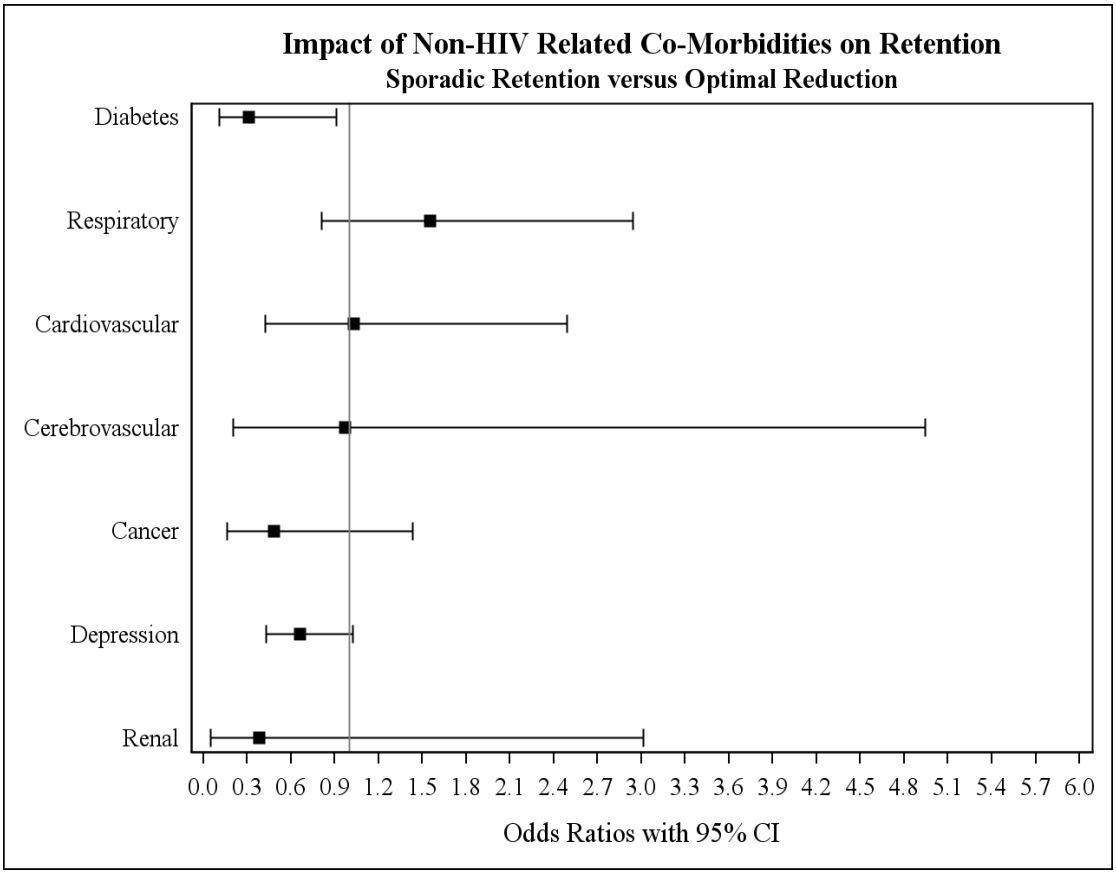

Figure 4.2 Forest plot diagram presenting the odds ratios from the multinomial logistic regression for sporadic retention versus optimal retention for each non-HIV related comorbid condition

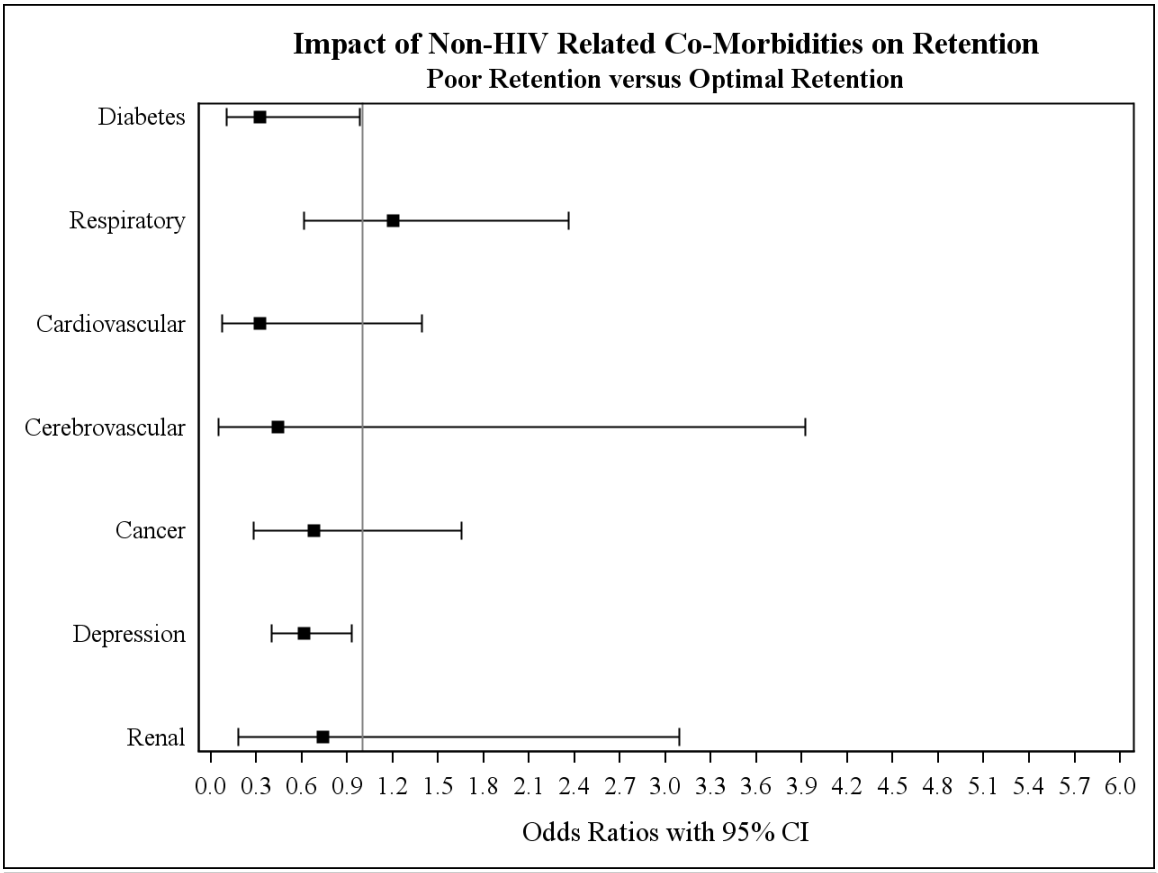

Figure 4.3 Forest plot diagram presenting the odds ratios from the multinomial logistic regression for poor retention versus optimal retention for each non-HIV related comorbid condition

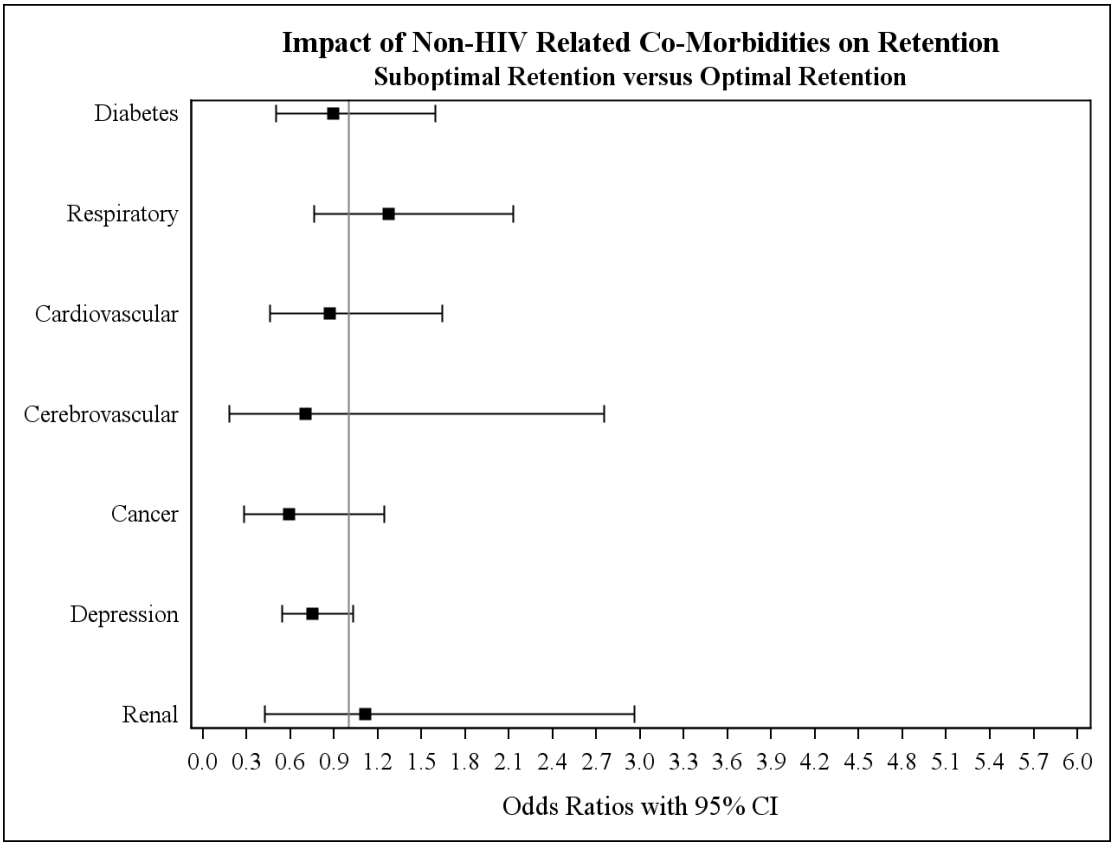

Figure 4.4 Forest plot diagram presenting the odds ratios from the multinomial logistic regression for suboptimal retention versus poor retention for each non-HIV related comorbid condition

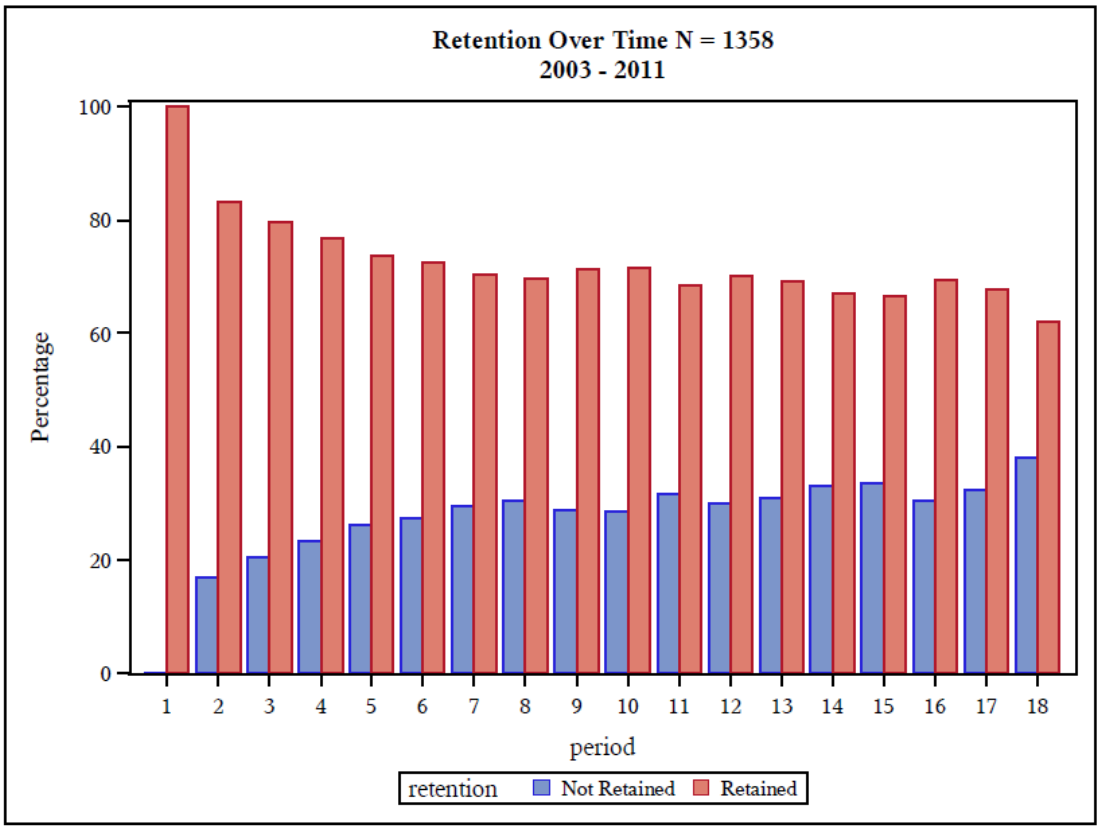

Figure 4.5 Plot of Retention over the study period among those individuals seeking HIV medical care from 2003 to 2011

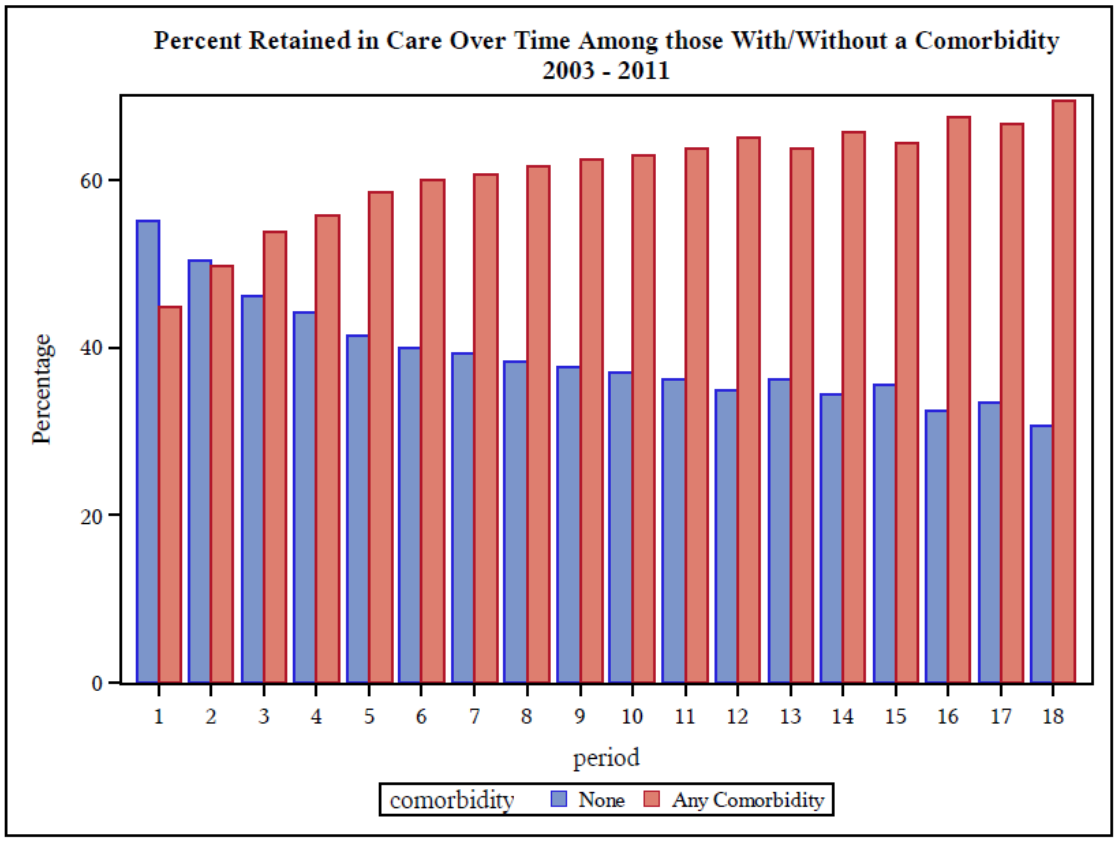

Figure 4.6 Plot of Retention over the study period among those individuals seeking HIV medical care with and without a non-HIV related Comorbidity diagnosed

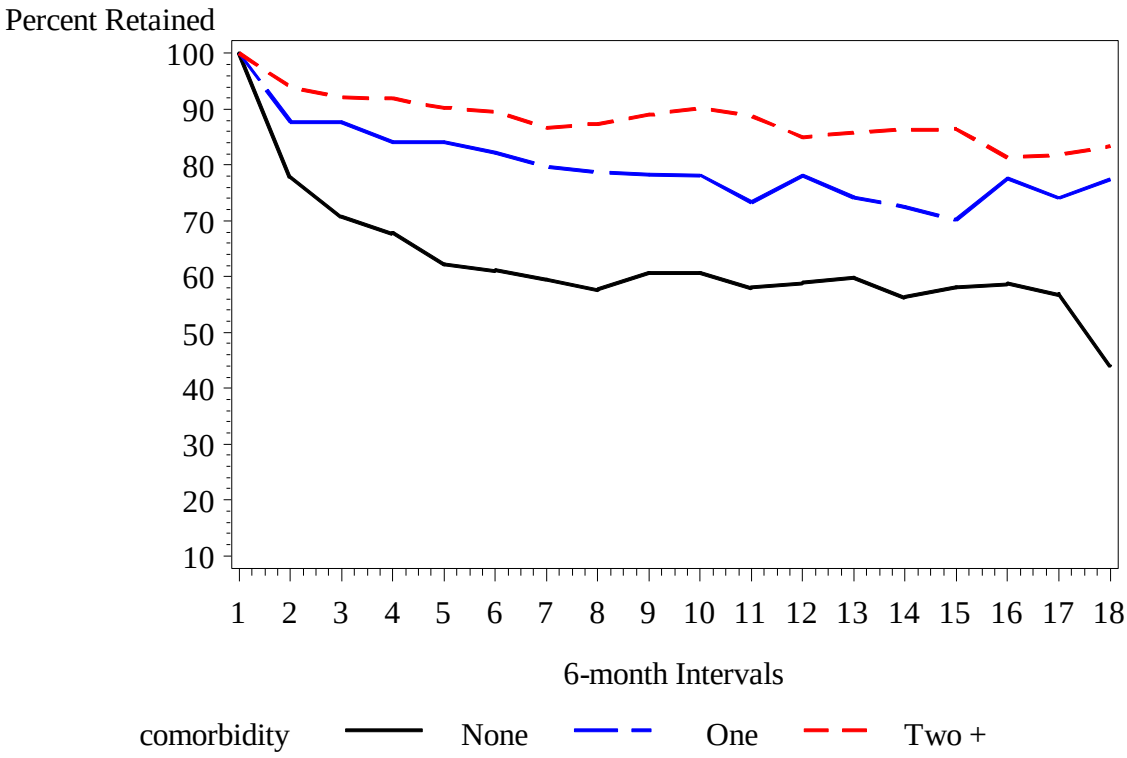

Figure 4.7 Plot of retention over the study period among those individuals seeking HIV medical care with none (black line), one (blue line), or two+ (red line) non-HIV related Comorbidities diagnosed

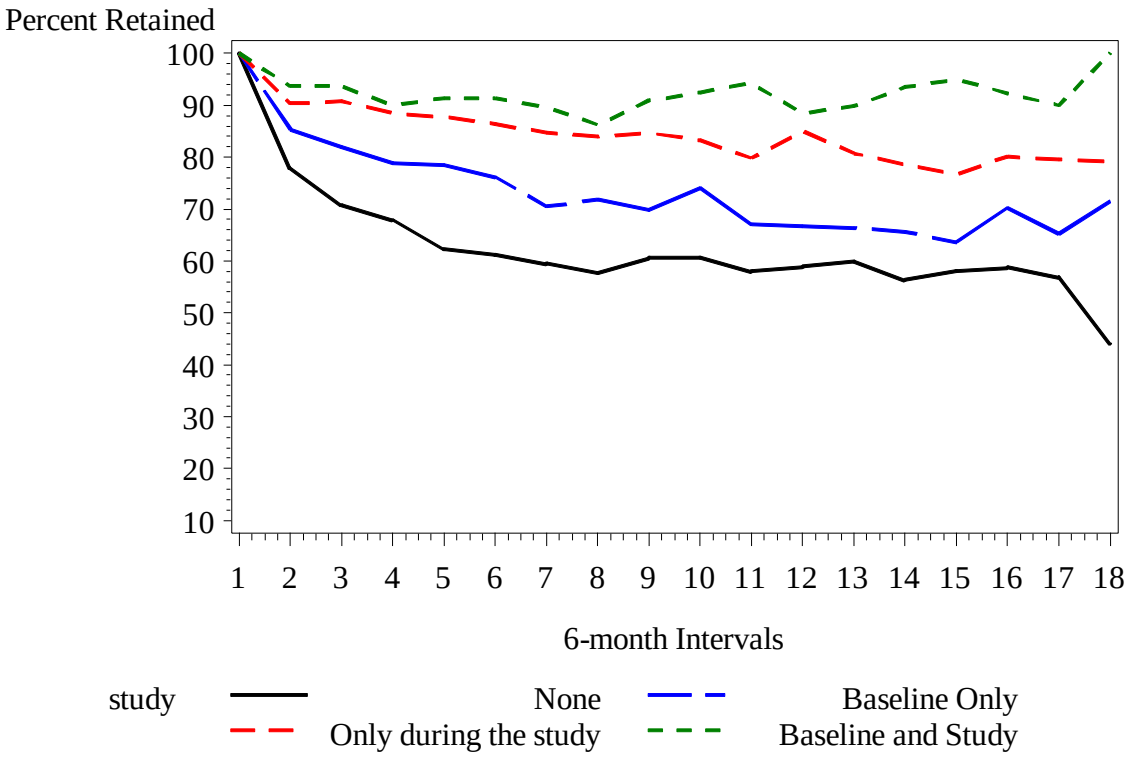

Figure 4.8 Plot of retention over the study period among those individuals seeking HIV medical care categorized by when the non-HIV related comorbidity was diagnosed. No comorbidity diagnosed (black line), comorbidity diagnosed at baseline only (blue line), comorbidity diagnosed only during the study period (red line), and comorbidity diagnosed at baseline and during the study period (green line)

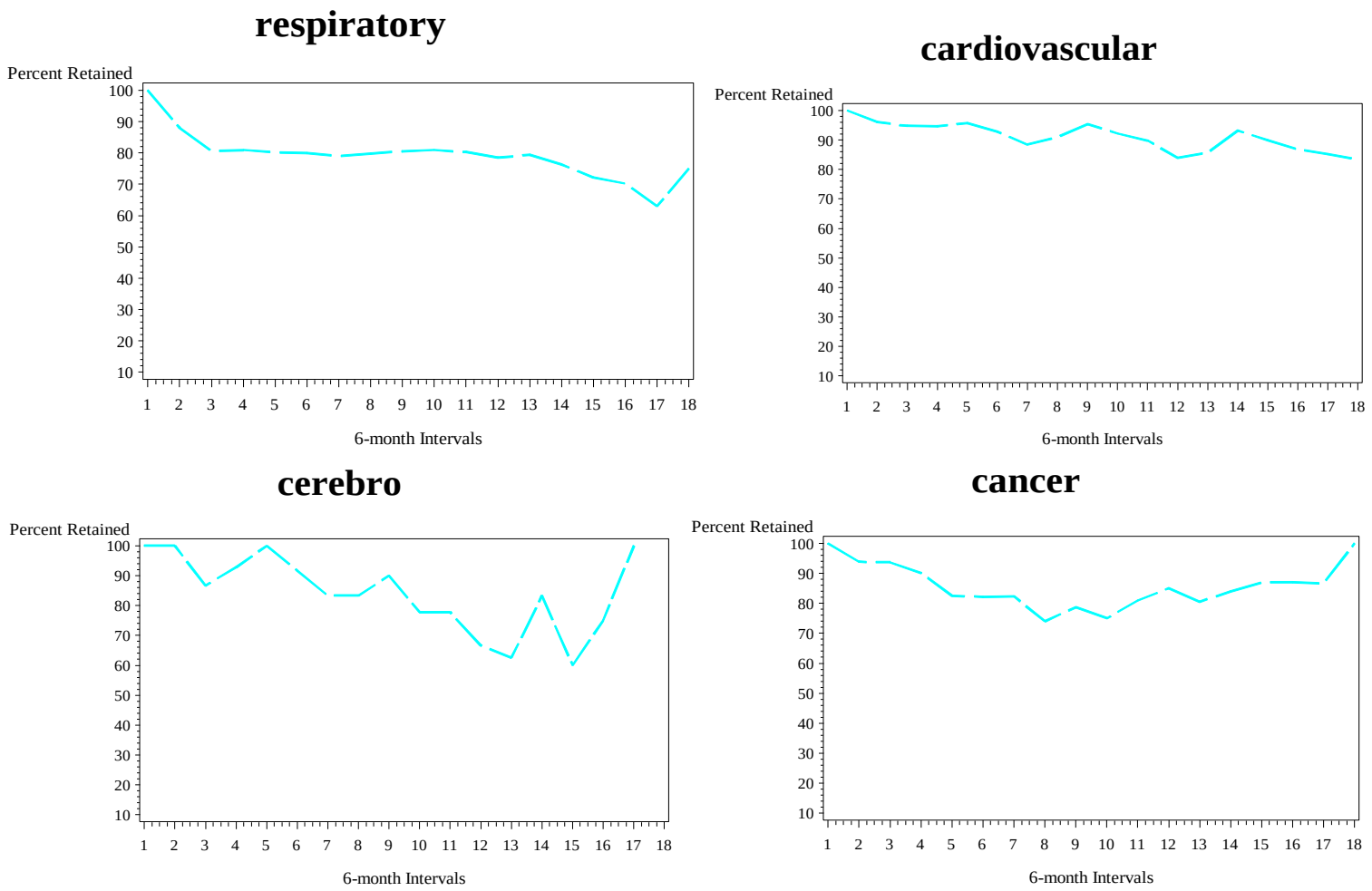

Figure 4.9 Plot of retention over the study period among those individuals seeking HIV medical care by the type of non-HIV related comorbidity diagnosed

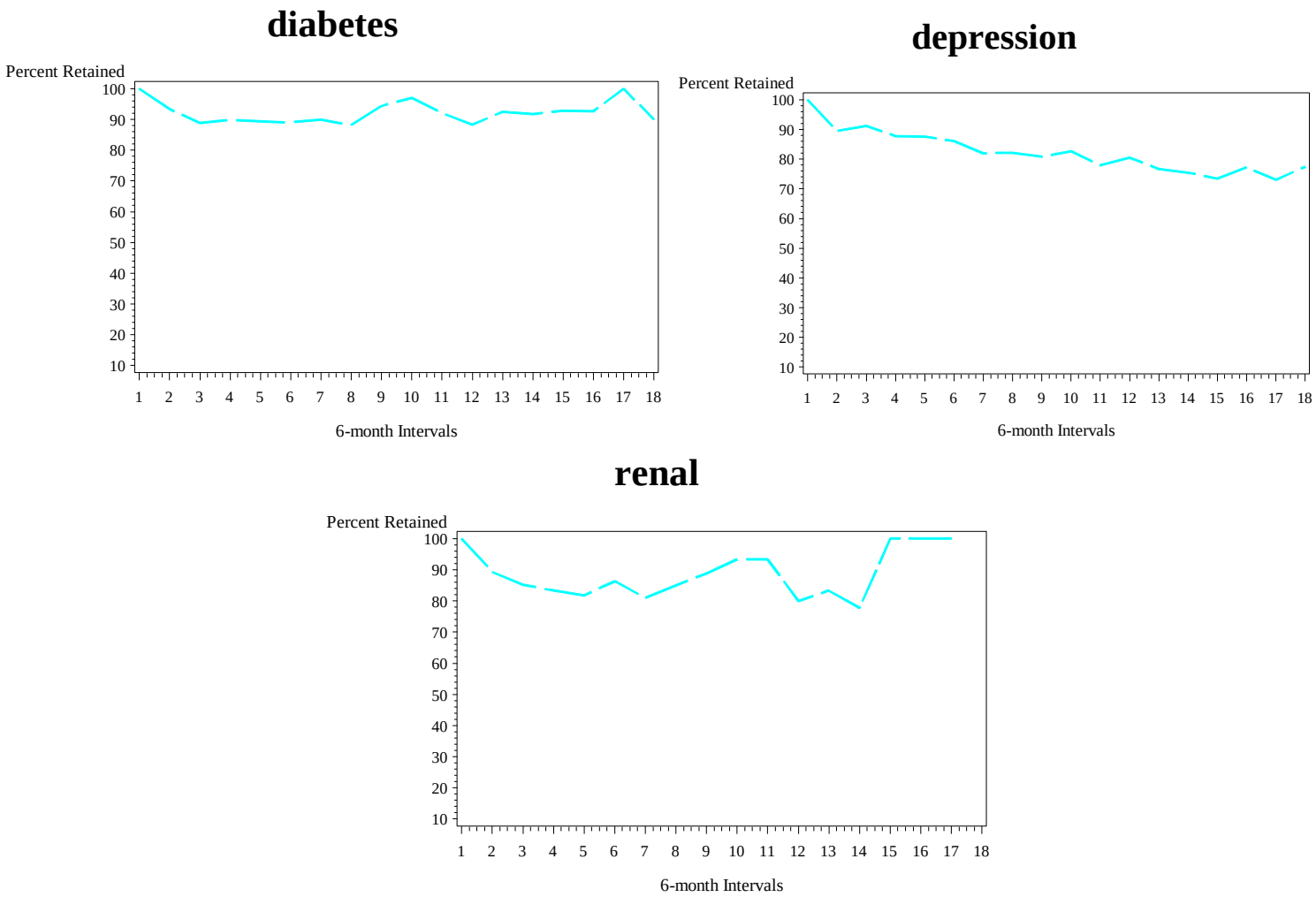

Figure 4.9 Continued

Chapter Five

Impact of Retention in HIV Medical Care on Time to Viral Load Suppression and Rebound among Individuals Initiating HAART

Introduction

Once an individual has been diagnosed with HIV, early linkage to and retention to continuous HIV medical care are arguably the two most important components to the continuum of HIV healthcare that improve the health outcomes of individuals diagnosed and living with HIV.[12] It has been suggested that in the United States (U.S.), approximately 77% of individuals diagnosed with HIV are linked into care within three to six months after diagnosis, but only 51% of those that are linked actually remain in care.[11] Maintaining optimal retention in medical care is required among individuals living with HIV to receive full access to all treatment benefits. Poor retention in care after initial linkage can be detrimental to an individual's health as this can delay the initiation of antiretroviral therapy and can lead to more detrimental clinical events, like virological failure, AIDS, or death.[22,25,27,28,85]

With the major advancements in HIV medical care, HIV has become a manageable chronic infectious disease. Initiating highly active antiretroviral therapy (HAART) into the clinical management of HIV has been shown to dramatically reduce the morbidity and mortality due to HIV, including suppressing viral load (VL) which in turn reduces the risk of HIV transmission.[24] Gardner et al suggested that approximately 25% of patients who are eligible to receive HAART are not receiving therapy due to refusal or failure to initiate therapy.[12] Of those who are receiving therapy, it is estimated that only 77% have achieved a viral suppression throughout the course of their infection. With approximately 15 to 25% of individuals without a suppressed VL, it is believed that barriers to achieving viral

suppression among individuals who have initiated HAART are poor medication adherence, non-persistence, and resistance.[12] Although this may be true, failure to maintain optimal retention in HIV medical care may play a significant role in the failure to achieve a suppressed VL.[24]

Poor retention in care represents an arduous obstacle to achieving viral suppression as this has important individual and public health implications. Little is known about the impact retention in care has on viral suppression, especially after individuals initiate HAART.[24,45,47] Understanding retention in care and how it affects health outcomes among individuals initiating HAART for the first time is very important. Individuals who have been linked to care and initiated HAART for the very first time are at a vulnerable stage in the course of their infection, as they are now expected to attend regularly scheduled clinic visits and sustain near perfect levels of medication adherence, and these individuals may not be prepared for the long-term commitment that is attached to HIV care.

A goal of the National HIV/AIDS strategy is to increase the proportion of HIV diagnosed persons with undetectable VL by 20%. That means, linking diagnosed persons into care, initiating therapy in a timely manner, and maintaining optimal retention throughout the course of infection.[59] But once an individual has achieved viral suppression, it is important that these individuals maintain suppression and avoid viral rebound. Achievement and maintenance of viral suppression is related to the long-term efficacy of HAART, but a large proportion of patients have viral loads rise above detectable levels over time. The rates of VL rebound have been reported to be between 20 and 40%.[95-98] High rates of VL rebound are typically among individuals with high VLs on starting HAART, but little is known on how retention in care impacts the time to virological rebound once suppression has been achieved.

The purpose of the study is to determine the impact retention in care has on viral suppression and rebound after initiating HAART. Employing parametric time to event methods, the hypotheses is that poor retention in care after initiation of HAART will delay time to viral suppression and shorten the time to viral rebound. This study extends prior research as it is one of the first studies to observe retention in care after initiation of HAART and to our knowledge is one of the first studies to evaluate the impact of retention on viral rebound.

Methods

Study Design

A retrospective cohort study design, employing a medical chart review, was conducted at an academic infectious disease clinic at the University of Kentucky (KY) to determine the impact retention in HIV medical care has on the time to viral suppression and viral rebound. Patients who sought care between January 1st, 2003 and May 1st 2011, and had initiated HAART anytime during the course of their infection, were considered eligible for this study, and were followed until December 31st, 2011. In this study, patients were followed from initiation of HAART until the event of interest occurred (viral suppression), or until the end of the study period (December 31st, 2011) or death. For the patients who achieved a viral suppression anytime during the study period, patients were followed from the time of suppression until the event of interest occurred (viral rebound), the end of the study period, or death. The study was approved by the University of KY Institutional Review Board.

Study Site

Individuals diagnosed with HIV and seeking HIV medical care at the Bluegrass Care Clinic (BCC) during the study period were considered for inclusion into the study. The BCC is a multi-disciplinary HIV care clinic located in an urban area in KY, and is the largest of four HIV care providers in a 63 county area in KY federally funded through the Ryan White HIV/AIDS Treatment and Modernization Act of 2006, and non-federal funds through the Commonwealth of KY. The BCC provides expert medical care by physicians, nurses, pharmacists, and other clinicians trained to deal with the complex management of a variety of infectious diseases, including HIV and related conditions. The BCC is home to approximately 2,000 active patients, which includes those living with HIV disease. Approximately 60% of the patient population lives in rural areas in KY.

Study Population and Eligibility

Data were abstracted from the HIV Lab Tracker™ electronic database. For the current study, patients who were seeking HIV medical care during the study period, were ≥18 years of age at the time of the study, and had initiated HAART at any time during the course of their infection were considered eligible for the study. To be included in the current study, patients had to have at least one HIV outpatient medical clinic visit during the specified study period (not including initiation of HAART), an initial VL measurement with an actual date of result, a subsequent VL measurement with an actual date attached, and a follow-up greater than 6 months. Restricting the study to patients that have a follow-up greater than 6 months allows time for patients to obtain a subsequent VL measurement so suppression can be observed.

For the time to viral suppression study, patients that had a VL measurement of <50 copies/ml at the time of the study were excluded from this analysis. For the time to viral rebound study, patients that did not achieve a viral suppression at any time during the study were excluded from the analysis. There were 1,166 patients that had initiated HAART and were eligible for the study, with 1,108 (95%) having at least one VL recorded. Of the 1,108 patients with at least one VL recorded, only 973 (88%) patients had a VL with a date recorded (Figure 5.1). There were no significant differences between those who did not have a date recorded and those who did.

For time to viral suppression, patients were excluded from the analysis of the study if they had achieved a suppressed VL (<50 copies/ml) prior to start of the study or the start of HAART. Of the 973 patients with a VL recorded during the study period, 549 (56%) had a VL that was >50 copies/ml at initiation of HAART and were included for the analysis. For time to viral rebound, patients were excluded from the analysis if they did not achieve a viral suppression at any time during the study period. Of the 973 patients, 699 (72%) had achieved at least one suppressed VL and was followed to observe viral rebound.

Study Measures

Demographic and clinical data were abstracted from the medical records for the patients included in the study. Demographic information collected during the study included date of birth, sex, race/ethnicity (white/nonwhite), marital status, employment status, insurance status, poverty level (<100% below federal poverty level), history of tobacco and illicit drug use (yes/no), and transmission category (Men who have Sex with Men (MSM), Heterosexual contact, Injection Drug Users (IDU), and other). The clinical characteristics obtained included $CD4^+$ cell counts, viral loads, concurrent HIV/AIDS

diagnosis, history of hepatitis c, history of hospitalizations, history of non-HIV related comorbidities, date of HAART initiation, and date of death.

Date of death was abstracted from the electronic medical records for those patients who sought care at the BCC during the study period. The Social Security Death Index was used to determine date of death for those patients who were lost to follow-up or had moved out of the service area. Each patient was manually entered into the database to determine date of death and was matched by name, date of birth, and social security number.

Retention in Care Measure

According to current Department of Health and Human Services guidelines, newly diagnosed individuals should seek HIV medical primary care at least every 3 to 4 months until their immunological and virological response has been maintained at the appropriate levels, and then once every 6 months after that.[23] Patients living with HIV who initiate HAART should be monitored consistently, so the patient can maintain adherence and viral suppression. Using visit constancy as the measure of retention in care for this study, patients' retention was dichotomized in optimal (100%) or non-optimal retainers (<100%).

Outcome Measures

The primary endpoint of the study was viral suppression, and was defined as having an HIV RNA level of <50 copies/ml. Time to viral suppression (years) was defined as the time from the initiation of HAART to the time of the first suppressed VL. Viral rebound was the secondary endpoint for this study and included only the individuals who achieved VL suppression at any time during the study period and was defined as having an HIV RNA level >1000 copies/ml.[97] Time to viral rebound (years) was defined as the time from viral suppression to the time of the first rebound.

Statistical Analysis

Descriptive statistics were produced to describe the study population by employing means, medians, standard deviations, and ranges to describe all continuous variables, and frequencies and percentages to describe all categorical variables. Independent two sample t-tests were used to detect differences in continuous variables, while chi-square tests were used to determine differences in categorical variables.

For the analysis of time to event data in most epidemiologic studies, in particular HIV studies, the Cox proportional hazards model has become the model of choice, but it has been argued that parametric methods such as the Accelerated Failure Time (AFT) model may provide a more appropriate modeling framework.[99,100] Advantages to employing parametric models are: 1) ability to use full maximum likelihood to estimate parameters; 2) the estimated coefficients can provide estimates that may be clinically meaningful; 3) estimates of survival time can be provided from fitted values from the model; and 4) residuals can be computed as differences between observed and predicted values of time.[100,101] To determine the impact retention has on time to viral suppression as well as viral rebound, parametric methods were employed.

In the time to event analysis for VL suppression, time was measured from the start of HAART and analysis time ended at the earliest date of a suppressed VL or the end of the study period or death. Those individuals who did not achieve VL suppression or died were censored at the end of the study. For time to VL rebound, time was measured from the date of first suppressed VL and analysis time ended at the earliest date of a VL rebound or the end of the study period or death. Those individuals that did not achieve a rebound were censored from the analysis. The Kaplan-Meier method was used to produce plots to provide useful information about the shape of the hazard function and the plots were used to also

determine whether the hazard function could be modeled using a parametric form. The log-survival and log-log survival plots were also produced to determine the appropriateness of a Weibull or Exponential distribution. Kaplan-Meier estimates were plotted overall and stratified by retention in care. For VL suppression, Wilcoxon tests were used to determine differences in survival curves between the retention groups and other covariates because it was assumed a priori that events would occur at earlier times and this test places more emphasis on the information at the beginning of the curves where the number at 'risk' is large.[100,101] For VL rebound, log rank tests were used to determine differences in survival curves. Producing Kaplan-Meier survival curves for all covariates of interest, we were able to obtain initial insight into the survival functions, which assisted in determining violation of the proportional hazards.[100]

The primary objective was not to determine just the risk of VL suppression, but to determine how early retention impacted time to VL suppression. Parametric survival models, in particular AFT models, were considered for the current analysis because the acceleration factor allows us to evaluate the effect of the predictor variables (retention) on the survival time as opposed to the hazard like the proportional hazard models.[100,101] Four parametric models were considered for this analysis (Exponential, Weibull, Log-Logistic, and Log-normal). All four models were fitted to the observed data and graphical evaluation of each parametric assumption was done which involved plotting the transformation of the Kaplan-Meier estimates against the log of time. If the plots produced a straight line, the parametric assumption was not violated.

To determine which parametric model was a better fit to the data, likelihood ratio tests were used to compare models which are nested within each other (i.e. Exponential, Weibull, and Lognormal) and Akaike Information Criteria (AIC) was used to compare the

models that were not nested within each other. Although one model may have a lower AIC compared to the other parametric models, Cox-Snell residual plots were produced to determine absolute goodness of fit for each model.

For time to VL suppression, the parametric model with the lowest AIC appeared to be the log-normal model. The Cox-Snell residual plot (Figure 5.2) presented a straight line suggesting the log-normal model was a good fit to the data. Variables with a *p*-value ≤0.15 in the univariate analysis were considered for inclusion into the final model. To determine how retention in care impacted time to viral suppression, the model controlled for insurance status, race, CD4+ cell counts at baseline, VL at baseline (log copies), income, history of AIDS, and year of HIV diagnosis. Time ratios were the measures of association for this analysis.

The same methods were used for observing time to VL rebound and the parametric model that appeared to have the better fit was the log-normal distribution (Figure 5.3). Time ratios (TR) were calculated for all variables included in the univariate and multivariate analysis. Variables with *p*-values ≤0.15 in the univariate analysis and those variables observed as confounders from previous literature were included in the multivariate analyses. The final model included retention in care, race, insurance status, history of AIDS, Hepatitis C, and an interaction between baseline VL and baseline CD4+ cell counts.

All data were analyzed using SAS version 9.3 (Cary, NC) and *p*-values <0.05 were regarded as statistically significant.

Results

Demographic Characteristics

For the study sample (n = 1,166), the mean age at the start of HAART was 39.0 years (STD = 9.8). The majority of the patients were men (81.2%) and white non-Hispanic (70.9%). The reported mode of transmission among the patients was MSM (58.2%), a large percentage of patients were employed (44.9%), but almost half of the patients were living below the federal poverty level (49.8%) (Table 5.1).

At the start of the study, approximately 40% of the patients did not have any form of insurance; with 33.3% having some form of public assistance (Medicaid or Medicare). Approximately 45% of the patients had an initial $CD4^+$ cell count <200 cells/μL and the mean log VL was 6.26 (3.01) copies. At the end of the study period, only 51.5% of the patients were optimally retained in care (Table 5.1). For the entire sample, 64% had achieved a suppressed VL during the study period (data not shown).

There were 549 (47%) patients that had a VL >50 copies/ml at the initiation of HAART and were followed to observe viral suppression. Of these, 275 (50.1%) patients achieved a viral suppression at least once during the study period. Those with a suppressed VL were more likely to be white non-Hispanic (76.4% versus 63.1%, p = 0.001), and those living above the federal poverty level (43.6% versus 29.6%, p = 0.001) (Table 5.2).

Clinically, those with a suppressed VL were more likely to have private insurance (29.9% versus 20.8%, p <0.0001) and Medicare (18.6% versus 7.7%, p <0.0001), an initial CD4+ cell count >350 cells/μL (44.0% versus 11.3%, p <0.0001), and more likely to have a lower mean log VL at initiation (8.4 copies versus 9.4 copies, p<0.0001). Viral suppression was also found to be more likely in those patients that optimally retained in care throughout the study period (62.6% versus 47.1%, p =0.0003) (Table 5.2).

At any time during the study period, 699 (60%) patients had achieved a viral suppression and were followed to observe a rebound. Of the 699 patients that achieved a VL suppression, approximately 22% (n=153) had a viral rebound during the course of the study. Those with a VL rebound were more likely to be those living below the poverty level (59.5% versus 43.6%, p = 0.001), and those with no insurance (39.2% versus 31.6%, p =0.003) or those on Medicaid (19.6% versus 14.4%, p=0.003). Clinically, viral rebound was significantly more likely to occur among those with a history of AIDS (69.9% versus 54.4%, p = 0.001), those with a history of Hepatitis C (18.3% versus 11.5%, p = 0.00), and those who were non-optimal retainers (59.5% versus 42.9%, p = 0.0003) (Table 5.2).

Time to Viral Suppression

Figure 5.4 presents the Kaplan-Meier curve for the 275 patients that achieved a viral suppression, with those patients who did not being censored (n = 274). The curve suggests a faster progression within the first year of initiation to HAART, followed by a much slower progression as time increases. The median time to viral suppression for the patients was approximately 5 years. Figure 5.5 presents a Kaplan-Meier curve of time to viral suppression stratified by retention. The curve suggests that the patients who were optimally retained in HIV medical care after the initiation of HAART had a shorter time to viral suppression compared to those who were not optimally retained in care. The median

time to viral suppression for optimal and non-optimal retainers was 2.5 and 6.5 years, respectively (Wilcoxon test, p <0.0001). The estimated cumulative survival distribution for the log-normal distribution was produced for optimal and non-optimal retainers. The curves, show results similar to the Kaplan-Meier curves, that optimal retainers have a higher chance of viral suppression compared to the non-optimal retainers (Figure 5.6).

In the log-normal models, the association with viral suppression was tested for all variables in the univariate models and those with a p-value <0.15 in the unadjusted model were included in the adjusted model. In the unadjusted log-normal model, non-whites, those with no insurance or Medicaid, those with an AIDS diagnosis, and higher baseline VLs, had longer times to viral suppression compared to their counterparts (Table 5.3). Controlling for insurance status, race, baseline CD4+ cell counts, and baseline VLs, the expected time to viral suppression for non-optimal retainers was 1.94 (95% CI: 1.37, 2.77) times greater than those who optimally retained in care. The expected time to viral suppression for those with no insurance was 1.68 (95% CI: 1.06, 2.68) times greater compared to those with private insurance, and those with higher baseline VL had a longer time to viral suppression (TR=1.11; 95% CI: 1.04, 1.19) (Table 5.3).

Time to Viral Rebound

The Kaplan-Meier curve for the 153 patients that experienced a viral rebound is presented in Figure 5.7. The figure appears to show a slow progression to viral rebound, and the mean time to rebound among the 153 patients was approximately 7 years. Stratified by retention in care, figures 5.8 and 5.9 shows the Kaplan-Meier curve and the estimated cumulative incidence curves for time to rebound curves for the lognormal distribution, respectively. The curves presented suggest that within the first few years of achieving viral suppression, the time to rebound is similar between the groups, but as time

progresses, individuals not optimally retained in care, have shorter time to rebound (Log Rank test, p = 0.013).

A log-normal regression model was chosen to determine the association between specific variables and time to viral rebound. Variables with a Log Rank test p-value ≤0.15 were initially included in the regression model. In the unadjusted analysis, retention in care, insurance status, AIDS diagnosis, Hepatitis C, CD4+ cell counts, VL were all associated with time to viral rebound (Table 5.4). Controlling for these variables, the expected time to viral rebound for those patients who were not optimally retained in care was 0.59 (95% CI: 0.38, 0.92) times shorter compared to those who were optimally retained. Compared to patients with private insurance, patients with no insurance or Medicaid had much shorter times to viral rebound at 0.42 (95% CI: 0.23, 0.76) and 0.42 (95% CI: 0.21, 0.83) times, respectively. There were no significant interactions with retention in care, but there was a significant interaction between baseline CD4+ cell count and baseline VL. As the baseline VL increases by one unit for patients with a baseline CD4+ cell count <200 cells/μL, the estimated time to viral rebound was 1.18 (95% CI: 1.00, 1.40) times longer compared to those with a baseline CD4+ cell count >200 cells/μL (Table 5.4). This result further suggests that individuals with a stable clinical status ('healthier') have worse outcomes compared to those entering care with much severe disease status.

Discussion

The purpose of this study was to understand the effect retention in care had on viral suppression and viral rebound among individuals receiving HAART. There is a paucity of research on the examination of the effect of retention in HIV medical care on time to viral suppression, and to our knowledge, this is one of the first studies to observe the impact retention has on viral rebound. For time to viral suppression, we selected a small cohort of

patients who were initiating HAART for the first time and followed them from the time of HAART initiation to the time of their first suppressed VL. Retention in care was shown to be associated with time to viral suppression. Patients that had optimal (100%) retention after initiating HAART were more successful at achieving a suppressed VL and the time it took to suppression was much shorter than the patients who were poorly retained in care. The results from our study are consistent with those of Mugavero et al, which observed the impact early retention (number of missed visits in the first year of care) had on viral suppression, and they were able to show that patients with perfect visit adherence were more likely to have a viral suppression, and that each "no show" clinic visit conveyed a 17% increased risk of delayed viral suppression.[24]

The results of the current study convey important implications for individual patient outcomes as well as future public health prevention efforts. Failure to achieve viral suppression in a timely manner and maintain a suppressed VL can be damaging to the individual's health; the longer it takes for an individual living with HIV to suppress their VL, the risk of detrimental clinical events increases. Researchers have suggested that failure to suppress one's VL can be an indicator of poor medication adherence as well as medication resistance.[12,85,95]

From a public health standpoint, failure to achieve viral suppression can be damaging to prevention efforts, as patients with high VLs may increase the risk of HIV transmission. In 2008, Metsch et al conducted a study to show how recently diagnosed patients with optimal early retention in care had reductions in sexual risk behaviors compared to those who were poorly retained.[31] We were able to show that poor retention in HIV care, among individuals who had initiated HAART, was a barrier for timely viral suppression, which in turn impedes the potential reduction of transmission of HIV to others.

This shows the importance of retention in care among individuals living with HIV and strategies should be developed to help re-engage those individuals who have fallen out of care as this can improve their chances of viral suppression.

Retention in care was also shown to be an important factor in an individuals' ability to maintain viral suppression after achieving their first suppressed VL. Of the 699 patients with a suppressed viral load at any time during the study period, approximately 22% rebounded back to a VL >1000 copies/ml and approximately 60% of the patients that rebounded had poor retention. The percentage of rebounders in our study is similar to other studies which observed VL rebound, ranging from 18% to 40%, but our study is unique as we observed the impact retention in care had on those who had a viral rebound.[96-98] The results of the study suggested that patients with optimal retention were more likely to prevent or at least prolong the time to a viral rebound. This is important as individuals who rebound after viral suppression suggest poor medication adherence as well as possible medication resistance, which typically leads to the stoppage of the specific drug class. This study notes the importance of retention in care even after the patient has achieved viral suppression. Once suppression has been achieved, the patient should still be retained in care and medication adherence should be monitored to prevent future viral rebound.

The patients in the study with no insurance or Medicaid had challenges in achieving timely viral suppression and prolonging viral rebound once VLs had been suppressed. Even when controlling for the other variables in the parametric models, patients with no insurance had delays in viral suppression and once VLs were suppressed they had shorter times to viral rebound. The cohort selected comes from a Ryan White funded clinic which means that there are opportunities available for individuals who are uninsured and may not

have resources to obtain their medications. This group of patients also had difficulties in retaining in care, which could explain why they did not suppress their VLs after initiation of HAART in a timely manner.

Patients on Medicaid were also more likely to acquire a viral rebound compared to those with private insurance. This is an interesting finding, as individuals on Medicaid can obtain medications and care for no charge. The Medicaid population has been consistently shown by researchers to be poor retainers in care, poor viral suppressers, and viral rebounders.[40,52,55] Studies should be conducted on this population to get a better sense of why retention is poor which can then lead to poor HIV outcomes. Understanding the factors that prevent this population from retaining in care and suppressing VLs can help guide future prevention efforts to re-engage this population back into care.

Monitoring patients living with HIV is important and care should be consistent before and after patients initiate HAART. We were able to show that patients with low CD4+ cell counts and high VLs at the time of initiation were more likely to delay viral suppression, and once suppressed, were more likely to progress to a viral rebound in a much shorter time period. Our results are consistent with other studies that have observed viral suppression and rebound.[24,97,98]

There is still the debate as to when a patient should start HAART based on their CD4+ cell count.[12] It appears that prescribing HAART at lower CD4+ cell counts in this population may be detrimental to the patients' health, but this shows the importance of maintaining consistent monitoring of these patients and making sure that they are engaged in care. Maintaining optimal retention among this cohort can lead to monitoring of medication adherence as well as referring to important ancillary services to help with treatment adherence and receipt of prescribed medications.

This study was an observational, retrospective cohort study and subject to potential uncontrolled confounders for which we had no information, such as alcohol use and presence of social and familial support networks. A medical chart review was employed to capture patient data and not all patients had complete information in their medical records. This was the case for selecting patients for inclusion into the study who had a VL and a follow-up measurement; 193 patients were excluded from the analysis partly because they had missing information regarding their HIV labs (e.g. VL recorded but no date, or a VL date but no VL result). There were no significant differences between those that were excluded from the analysis, but exclusion of subjects reduces the power of the study and potentially introduces bias. Although the BCC provides care for a large proportion of individuals diagnosed with HIV who reside in central and eastern KY, the results may not be generalizable to all Kentuckians living with HIV nor all individuals living with HIV in the United States. A future research study conducted using similar methods should involve a multi-center study across all Ryan White funded clinics in KY.

Finally, medication adherence was not observed or evaluated for this study. Studies have observed the impact medication adherence has on viral suppression as well as viral rebound, and have suggested that patients that are not at least 95% adherent to their medications are more likely to have virological failures. Medication adherence is on the causal pathway between retention in care and VL suppression/rebound, but the purpose of this study was to establish the relationship between retention and VL suppression and rebound.[19] It may be concluded that medication adherence is the driving force behind viral suppression, but Giordano et al were able to show that poor retention in care and poor medication adherence were highly correlated therefore it seemed appropriate to use retention in care as a surrogate measure.[85] Also with this study, obtaining medication adherence was difficult as the patient population at the BCC obtain their medications from

multiple pharmacies, which makes it difficult to track medication pick up once the prescription has been written. If there was a centralized pharmacy available for this population, medication adherence could be evaluated more accurately. The retention in care measurements were subject to very little if any measurement error, since our medical records on patient clinic visits were excellent.

Conclusion

In conclusion, we were able to identify significant associations between retention in care and viral suppression/rebound among patients initiating HAART. Patients who were poorly retained in care after initiating HAART prolonged their opportunity to achieve viral suppression compared to optimal retainers in care. And, once the VL was suppressed, poor retainers had shorter times to viral rebound compared to optimal retainers in HIV medical care. The results of this study stress the importance of maintaining optimal retention among individuals living with HIV in order to increase the number of individuals with suppressed VLs. Researchers should continue to study the impact of retention in HIV medical care on clinical outcomes and strategies to improve retention and re-engage those lost to follow-up back into care.

Table 5.1. Socio-demographic and Clinical Characteristics among Patients Initiating HAART

	Total n (%)
Total	1166 (100)
Sex	
Female	219 (18.8)
Male	947 (81.2)
Race	
Non-White	339 (29.1)
White	827 (70.9)
Age at HAART	
≤24 yrs	89 (7.6)
25 - 34 yrs	294 (25.2)
35 - 44 yrs	453 (38.9)
>44 yrs	330 (28.3)
Age mean yrs (std)	39.0 (9.8)
Mode of Transmission	
Heterosexual	328 (28.2)
IDU	100 (8.6)
Other	59 (5.1)
MSM	678 (58.2)
Employment Status	
Employed	441 (44.9)
Unemployed	350 (35.6)
Other	191 (19.5)
Poverty Level	
Below	581 (49.8)
Above	405 (34.7)
Missing	180 (15.4)
History of Tobacco Use	
Yes	580 (49.7)
No	586 (50.3)
History of Illicit Drug Use	
Yes	301 (25.8)
No	865 (74.2)

Table 5.1. continued

	Total n(%)
Insurance Type	
No Insurance	465 (40.3)
Medicaid	188 (16.3)
Medicare	196 (17.0)
Private	304 (26.4)
History of AIDS Diagnosis	
Yes	688 (59.0)
No	478 (41.0)
Hepatitis C	
Yes	149 (12.8)
No	1017 (87.2)
Non-HIV related comorbidity	
Yes	571 (49.0)
No	595 (51.0)
Baseline CD4+ Cell Counts	
<200	359 (44.8)
200 - 350	142 (15.7)
>350	406 (34.8)
Baseline CD4+ Cell Counts - Median (min, max)	322 (1.0, 1696)
Baseline Viral Load mean log copies (std)	6.69 (3.10)
Retention	
Optimal	601 (51.5)
Non Optimal	565 (48.5)

Table 5.2. Associations of Socio-Demographic and Clinical Characteristics and Viral Suppression and Rebound among the Patients Seeking HIV Medical Care and Initiating HAART

	Viral Suppression (n = 549)			Viral Rebound (n = 699)		
	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p
Total	275 (50.1)	274 (49.9)		153 (21.9)	546 (78.1)	
Sex						
Female	52 (18.9)	58 (21.2)	0.51	32 (20.9)	90 (16.5)	0.2
Male	223 (81.1)	216 (78.8)		121 (79.1)	456 (83.5)	
Race						
Non-White	65 (23.6)	101 (36.9)	0.001	41 (26.8)	117 (21.4)	0.16
White	210 (76.4)	173 (63.1)		112 (73.2)	429 (78.6)	
Age at HAART						
≤24 yrs	20 (7.3)	19 (6.9)	0.20	5 (3.3)	20 (3.7)	0.28
25 - 34 yrs	67 (24.4)	89 (32.5)		38 (24.8)	107 (19.6)	
35 - 44 yrs	13 (41.1)	103 (37.6)		65 (42.5)	217 (39.7)	
>44 yrs	75 (27.3)	63 (23.0)		45 (29.4)	202 (37.0)	
Age mean yrs (std)	38.9 (9.6)	37.7 (9.3)	0.14	39.2 (9.0)	40.3 (9.7)	0.18
Mode of Transmission						
Heterosexual	75 (27.3)	85 (31.1)	0.69	43 (28.1)	150 (27.5)	0.33
IDU	26 (9.5)	22 (8.1)		16 (10.5)	46 (8.4)	
Other	10 (3.6)	12 (4.4)		11 (7.2)	23 (4.2)	
MSM	164 (59.6)	154 (56.4)		83 (54.3)	327 (59.9)	
Employment Status						
Employed	109 (45.0)	106 (47.3)	0.04	54 (38.6)	220 (46.5)	0.2
Unemployed	78 (32.2)	87 (38.8)		54 (38.6)	149 (31.5)	
Other	55 (22.7)	31 (13.8)		32 (22.9)	104 (22.0)	
Poverty Level						
Below	135 (49.1)	154 (56.2)	0.001	91 (59.5)	238 (43.6)	0.001
Above	120 (43.6)	81 (29.6)		52 (34.0)	226 (41.4)	
Missing	20 (7.3)	39 (14.2)		10 (6.5)	82 (15.0)	
History of Tobacco Use						
Yes	150 (54.6)	143 (52.2)	0.58	86 (56.2)	265 (48.5)	0.09
No	125 (45.5)	131 (47.8)		67 (43.8)	281 (51.5)	
History of Illicit Drug Use						
Yes	86 (31.3)	86 (31.4)	0.98	29 (19.0)	127 (23.3)	0.26
No	189 (68.7)	188 (68.6)		124 (81.1)	419 (76.7)	

Table 5.2. continued

	Viral Suppression			Viral Rebound		
	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p
Insurance Type						
No Insurance	108 (39.4)	145 (52.9)	<0.001	60 (39.2)	171 (31.6)	0.003
Medicaid	33 (12.0)	51 (18.6)		30 (19.6)	78 (14.4)	
Medicare	51 (18.6)	21 (7.7)		37 (24.2)	119 (22.0)	
Private	82 (29.9)	57 (20.8)		26 (17.0)	174 (32.1)	
History of AIDS Diagnosis						
Yes	165 (60.0)	184 (67.2)	0.08	107 (69.9)	297 (54.4)	0.001
No	110 (40.0)	90 (32.9)		46 (30.1)	249 (45.6)	
Hepatitis C						
Yes	38 (13.8)	37 (13.5)	0.91	28 (18.3)	63 (11.5)	0.03
No	237 (86.5)	237 (86.2)		125 (81.7)	483 (88.5)	
Non-HIV related comorbidity						
Yes	143 (52.0)	120 (43.8)	0.05	99 (64.7)	300 (55.0)	0.03
No	132 (48.0)	154 (56.2)		54 (35.3)	246 (45.1)	
Baseline CD4+ Cell Counts						
<200	100 (36.4)	131 (47.8)	<0.001	36 (23.5)	126 (23.1)	0.06
200 - 350	53 (19.3)	22 (8.0)		30 (19.6)	88 (16.1)	
>350	121 (44.0)	31 (11.3)		84 (54.9)	289 (52.9)	
Missing	1 (0.4)	90 (32.9)		3 (2.0)	43 (7.9)	
Baseline Viral Load mean log copies (std)	8.4 (2.8)	9.4 (2.5)	<0.001	5.7 (2.67)	5.8 (2.9)	0.89
Early Retention						
Optimal	172 (62.6)	129 (47.1)	<0.001	62 (40.5)	312 (57.1)	<0.001
Non Optimal	103 (37.5)	145 (52.9)		91 (59.5)	234 (42.9)	

Table 5.3 Log-normal Regression Determining the Association between Retention in HIV Medical Care and Time to Viral Suppression

Variables	Unadjusted TR[a]	95% CI[b]	Adjusted TR	95% CI
Retention				
Non Optimal vs. Optimal	**2.31**	**(1.62, 3.31)ǂ**	**1.94**	**(1.37, 2.77)ǂ**
Race				
Non-White vs. White	**1.69**	**(1.13, 2.52)***	1.34	(0.91,2.00)
Insurance Status				
No Insurance vs. Private	**1.70**	**(1.09, 2.64)***	**1.68**	**(1.06, 2.68)***
Medicaid vs. Private	**2.15**	**(1.19, 3.89)***	1.56	(0.83, 2.94)
Medicare vs. Private	0.97	(0.54, 1.74)	0.82	(0.46, 1.46)
Poverty Level				
Above vs. Below	**0.68**	**(0.41, 0.99)***	1.02	(0.67, 1.55)
Baseline CD4+ Cell Counts (per 100 cells/μL)	**0.84**	**(0.79, 0.91)ǂ**	**0.89**	**(0.81, 0.97)ǂ**
AIDS Diagnosis				
Yes vs. No	**1.86**	**(1.29, 2.68)†**	1.23	(0.79, 1.91)
Baseline Viral Load (per log copy/ml)	**1.11**	**(1.04, 1.19)†**	**1.11**	**(1.04, 1.19)†**

[a] TR = Time Ratio

[b] CI = Confidence Interval

ǂ p-value <0.0001

† p-value <0.01

* p-value <0.05

Note: The Regression model adjusted for the year of HIV diagnosis

Table 5.4 Log-normal Regression Determining the Association between Retention in HIV Medical Care and Time to Viral Rebound

Variables	Adjusted TR	95% CI
Retention		
Non Optimal vs. Optimal	**0.59**	**(0.38, 0.92)**
Race		
Non-White vs. White	0.72	(0.43, 1.19)
Insurance Status		
No Insurance vs. Private	**0.42**	**(0.23, 0.76)**†
Medicaid vs. Private	**0.42**	**(0.21, 0.83)**†
Medicare vs. Private	0.56	(0.30, 1.05)
AIDS Diagnosis		
Yes vs. No	**0.47**	**(0.28, 0.77)***
Hepatitis C		
Yes vs. No	1.23	(0.68, 2.24)
Baseline Viral Load		
Baseline CD4+ Cell Count <200	**1.18**	**(1.00, 1.40)***
Baseline CD4+ Cell Count >200		

[a] TR = Time Ratio

[b] CI = Confidence Interval

ǂ p-value <0.0001

† p-value <0.01

* p-value <0.05

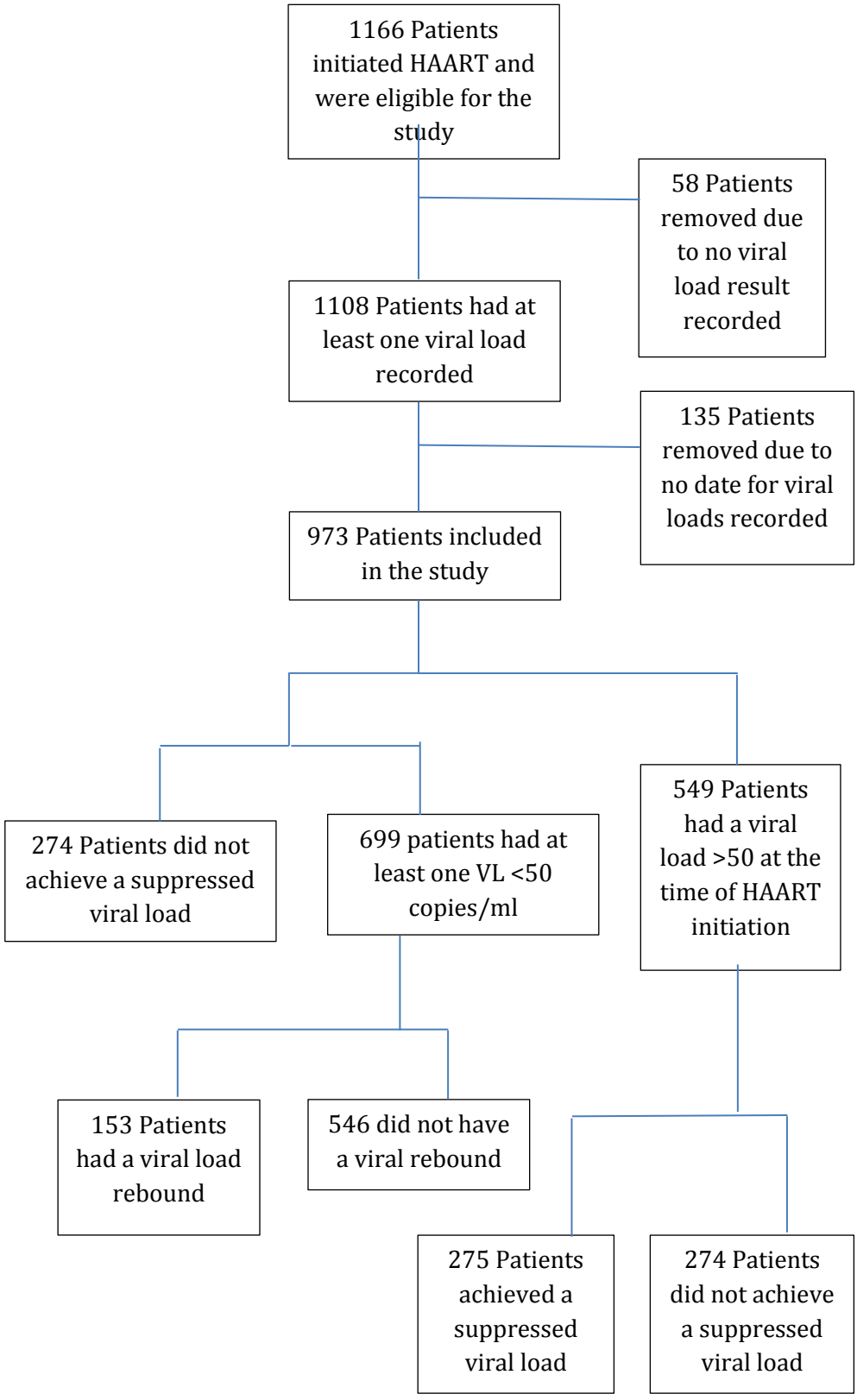

Figure 5.1 Flow chart of the Patients Enrolled in the Study

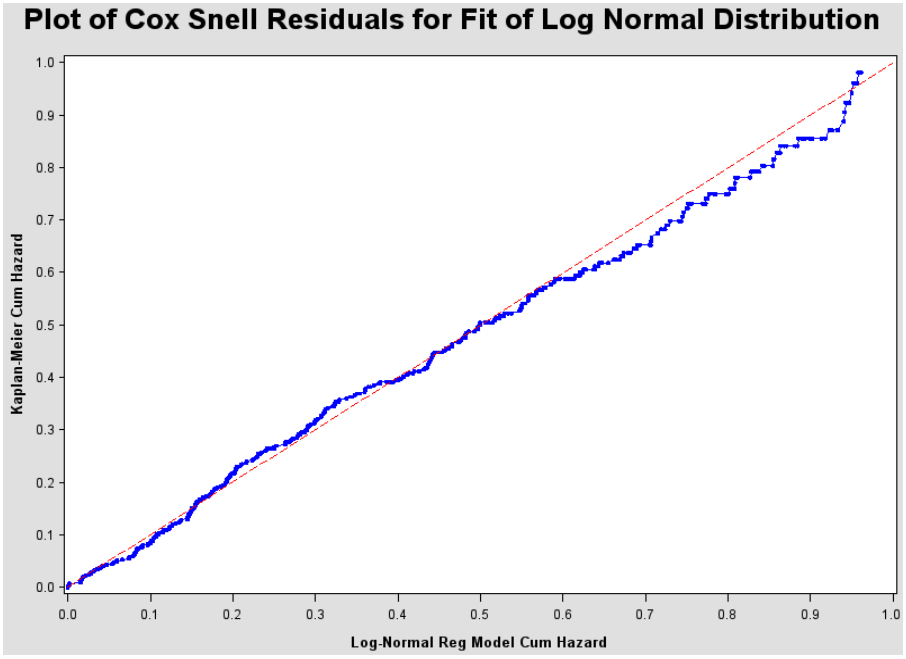

Figure 5.2 Cumulative Hazard Plot of the Cox-Snell Residual for the Log-Normal Model Determining Time to Viral Suppression

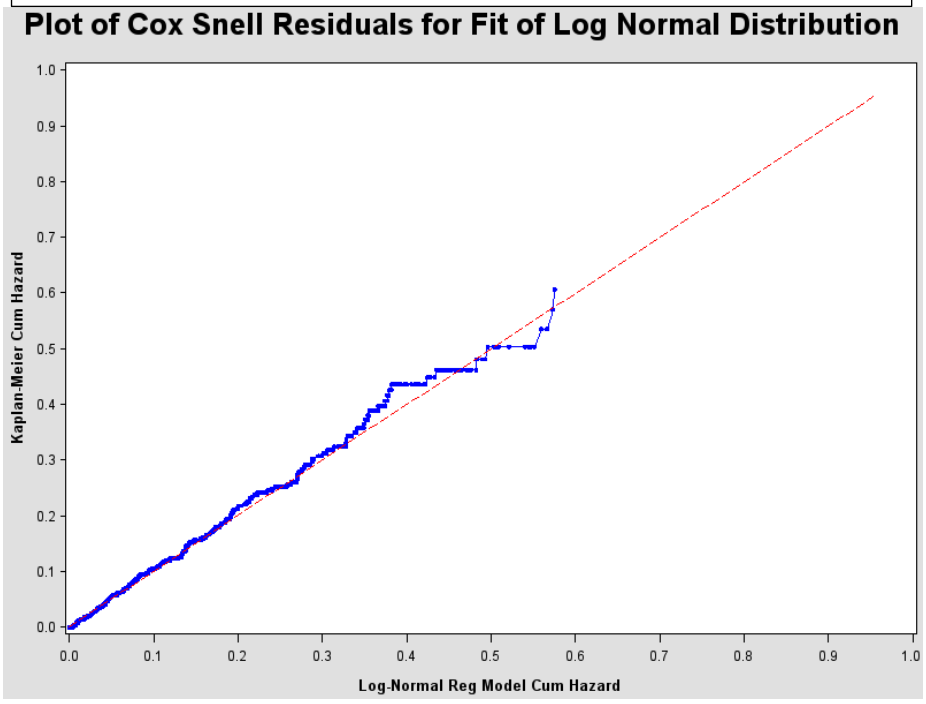

Figure 5.3 Cumulative Hazard Plot of the Cox-Snell Residual for the Log-Normal Model Determining Time to Viral Rebound

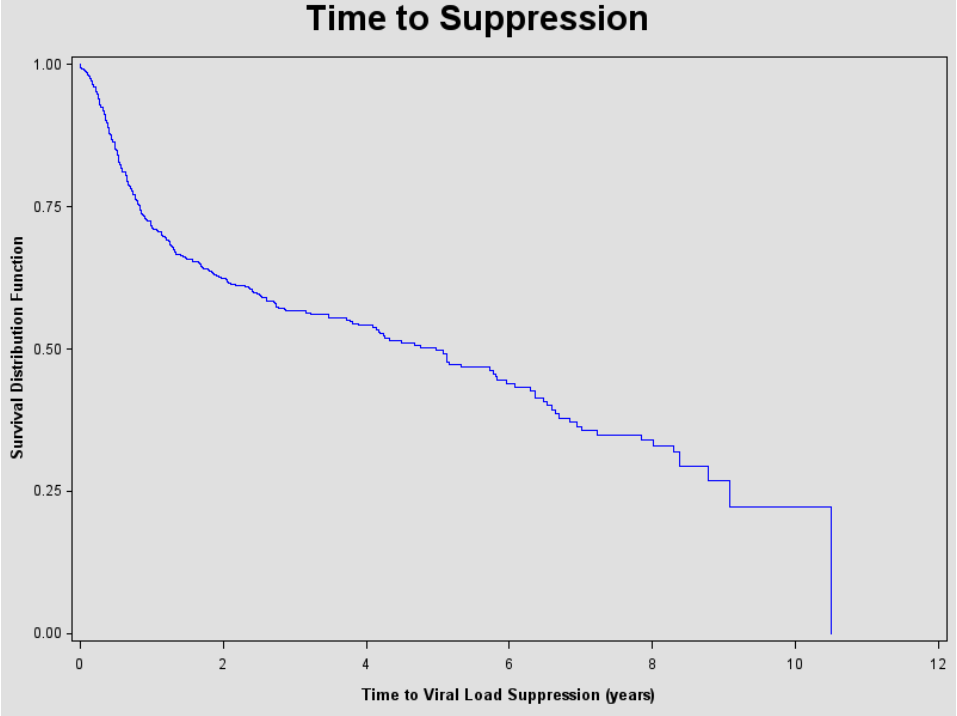

Figure 5.4 Kaplan-Meier Curve for the Time to Viral Suppression

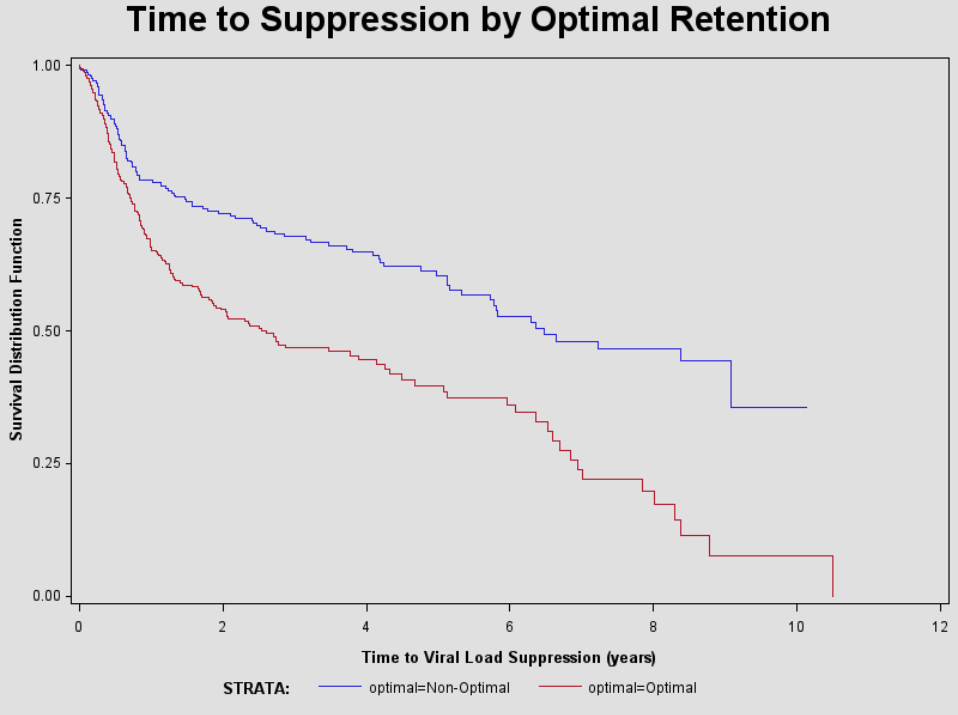

Figure 5.5 Kaplan-Meier Curves for the Time to Viral Suppression Stratified by Optimal Retention

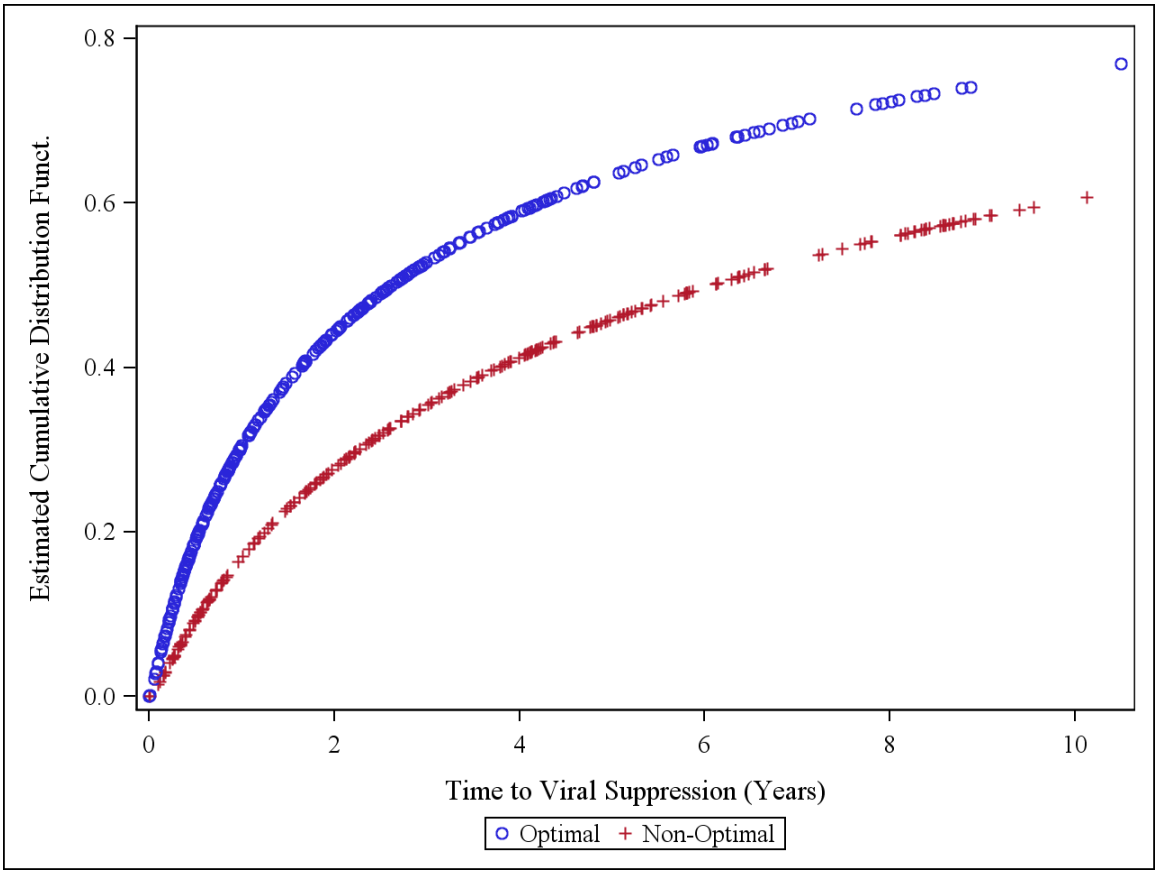

Figure 5.6 Estimated Cumulative Incidence Curves for time to viral suppression for the Log-Normal distribution

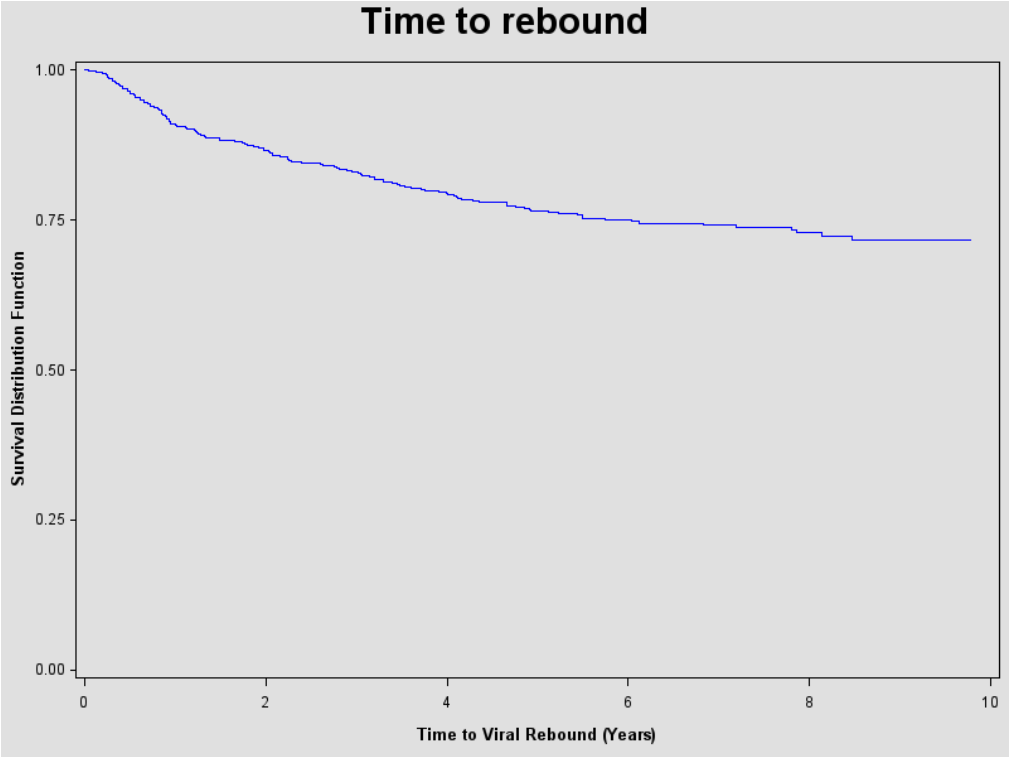

Figure 5.7 Kaplan-Meier Curves for Time to Viral Rebound

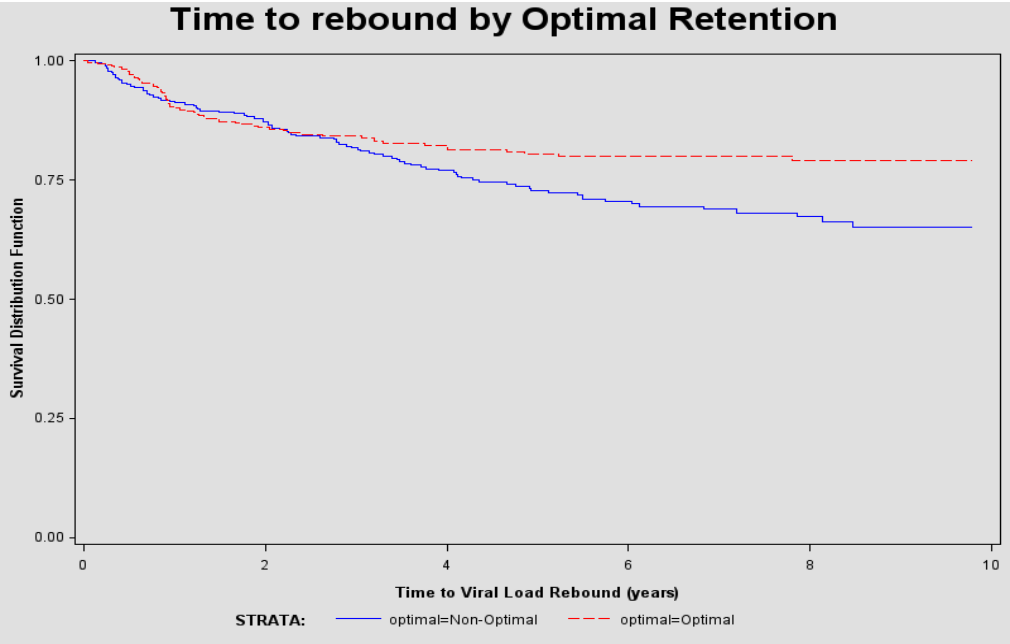

Figure 5.8 Kaplan-Meier Curves for Time to Viral Rebound Stratified by Optimal Retention

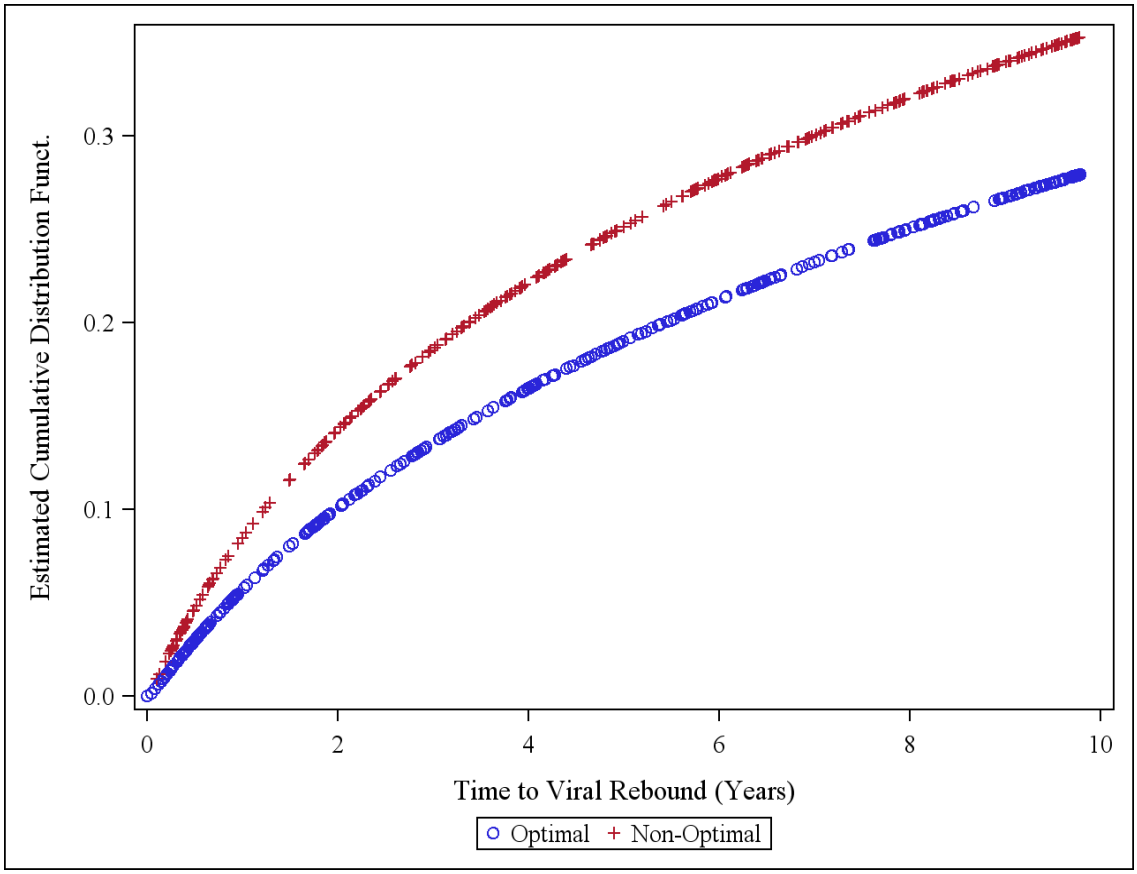

Figure 5.9 Estimated Cumulative Incidence Curves for time to viral rebound for the Log-Normal distribution

Chapter Six

Discussion and Conclusion

This chapter provides a summary and discussion of the conclusions of the five previous chapters. This chapter also discusses the individual and public health implications, the strengths and limitations of this research, and recommendations for future research. There were four papers presented in this dissertation: (1) Measuring Retention in HIV Medical Care: A Literature Review; (2) "A Comparison Study of Methods for Measuring Retention in HIV Medical Care"; (3) "Impact of non-HIV Related Comorbidities on Retention in HIV Medical Care: Does Retention Improve over Time"; and (4) "Impact of Retention in HIV Medical Care on Time to Viral Load Suppression and Rebound among Individuals Initiating HAART."

The first paper (Chapter Two) was a comprehensive literature review that focused on the methods used in measuring retention, their advantages and disadvantages, and their predictors. The purpose of the review was to provide the reader with a framework of how the retention measures have been conducted in studies and what resources are needed to evaluate retention. The review showed that there were at least five different ways to measure retention in care among individuals living with HIV. The five measures were visit constancy, gaps in care, missed visits, visit adherence, and the HRSA performance measure[15]. The choice of a retention measure may depend on the data and resources available to the clinicians or researchers[15]. The retention studies, regardless of the measure used, show that in general, approximately 60% of patients were actually retaining in care and the predictors observed were similar, regardless of the time period[13]. Currently, there has no study to suggest which retention measure should is preferred.

In chapter three, the purpose was to measure retention in HIV medical care by employing three measurement techniques (visit constancy, gaps in care, and the HRSA performance measure). The three techniques were compared, using ROCs, to determine which methods most accurately discerned between those patients with and without a viral suppression or CD4+ cell count failure. The patients included in the study were followed for an average of 5 years and the average retention was approximately 77.6% and 77.2% for visit constancy and the HRSA performance measure, respectively. The average time between two consecutive visits was 8 months. Calculating and comparing the AUCs among the three measures, visit constancy appeared to be the best measure in predicting viral suppression as it had the highest AUC. The logistic regression performed in this study showed that there was a dose-response in regards to the impact retention had on achieving viral suppression. Patients who were suboptimal, sporadic, or poor retainers had much lower odds of achieving viral suppression compared to those with 100% retention (optimal).

Currently there is no preferred method for defining retention in care as multiple methods have been used in the research, but the purpose of this study was to determine which method may be the most appropriate measure as this could help clinicians and researchers to be more consistent in choosing a measurement. Having consistency in the way retention is measured increases the ability to accurately compare across research studies.

Chapter Four focused on the predictors of retention in HIV medical care as well as how non-HIV related comorbidities impacted retention over time. There have been inconsistent results on how comorbidities like mental health disorders impact retention in care. This study was one of the first studies to observe how multiple comorbidities

diagnosed during the course of infection impacted retention over time. The 1,358 patients included in the study were followed in 6-month intervals to determine the number of clinic visits completed and the diagnoses of any comorbidity or other infections. There were seven comorbidities observed in this study (cardiovascular, cerebrovascular, diabetes, mental health, respiratory, cancer, and renal). Using visit constancy as the retention measure of choice, the patients were categorized into four groups: optimal retainers, suboptimal retainers, sporadic retainers, and poor retainers.

Only 48.6% of the patients included in the study had optimal retention throughout the entire study. It was also shown retention decreased over time for the cohort, especially for those who did not have any comorbidity or other illnesses. A GLMM was employed to show that patients with one or more comorbidities diagnosed throughout the study period had improved retention over time. Looking at each comorbid condition separately, patients with diabetes, cancer, cardiovascular, and depression conditions had improved retention over time compared to their counterparts. It was also shown that non-whites, those with an ADI, those with Hepatitis C, and those with no insurance or Medicaid had worse retention over time compared to their counterparts.

Chapter Five focused on how retention in care impacted time to viral suppression and viral rebound among individuals who initiated HAART. There were 1,166 patients that had initiated HAART during the study period, and were followed from the time of HAART initiation until the time of viral suppression. This study was conducted because little is known on how retention in care impacts the time to viral suppression and rebound among those who are poorly retained in care.

It was shown that individuals who retained in care after initiation of HAART were more likely to achieve viral suppression and had a shorter time to progression compared to those who did not optimally retain in care. It was also shown that among those who achieved a viral suppression, optimal retention prolonged the risk of viral rebound.

Implications

The results from these studies have major implications for the individuals living with HIV as well as public health efforts. The results are consistent with other studies conducted. It is important to note how important retention in care is on the health of an individual living with HIV. It was shown that individuals poorly retained in care had prolonged times to viral suppression and increased risk of viral rebound once suppression had been achieved. This is important, as viral suppression is typically used as a surrogate measure for determining HIV management success as well as medication adherence. Individuals not retaining in care continuously are missing opportunities for accessing treatment benefits and increasing their risk for medication resistance, progression to AIDS, and death.

From a public health perspective, poorly retained HIV infected individuals can hinder the process in reducing the incidence of HIV in Kentucky as well as in the U.S. It is estimated that approximately 50,000 people are infected with HIV each year in the U.S., and researchers have suggested the use of retention and engagement in HIV care as a prevention tool to reduce this statistic.[11,12,72]

It has been shown that optimal retention in care can reduce risky sexual behaviors and even reduce the risk of HIV transmission. These study results clearly showed that optimally retaining in care increases viral suppression and reduces risk of viral failure. If we can engage all individuals living with HIV in continuous care, the burden of VL will be decreased and the chances of transmission will be reduce.

Strengths and Limitations

A major strength of these studies is the comparatively long study period (9 years). The average follow-up time for the patients included in the study was approximately 5 years, which allowed for evaluation of retention over time. The dissertation adds to the current literature by comparing multiple measures of retention and using an extended time period to assess the effects of retention in care over time.

The study population observed in this study was patients who sought care at a RW funded clinic (BCC) in Lexington, Kentucky. The BCC is home to approximately 2,000 active patients and a large percentage of those seeking care at the clinic are from rural areas in Kentucky, the findings may not be generalizable to all individuals living with HIV/AIDS who are seeking medical care in Kentucky or in the U.S. There may be significant differences, other than insurance and income status, between those seeking care in RW funded clinics and those seeking care in private clinics in Kentucky. Currently no studies have compared RW funded clinics with other HIV care clinics in the U.S.

The studies conducted in this dissertation were retrospective cohort studies, which employed a medical chart review. Uncontrolled confounders may exist for which no information was available. Medical charts are not designed for research purposes and information was incomplete for some (or most) of the patients seeking care; this was the

case for demographic information like education and income. Also VLs and CD4+ cell counts were missing for a number of patients that sought care at the BCC; therefore they could not be included in some of the study analyses. Although there were no major differences between the groups excluded and included from the analyses, other than the fact that those excluded were not on HAART, those that were excluded reduced the power of the study to observe differences across groups and may have introduced biases.

As noted in Chapter Two, there are at least five ways to measure retention in HIV medical care (visit constancy, HRSA performance measure, visit adherence, missed visits, and gaps in care), but only three of the five measurements were evaluated in this dissertation. A limitation is that visit adherence and missed visits were not evaluated and compared to the other three measures, in part because missed clinic visits were not captured in the medical charts. In order to determine the number of visits that were missed and calculate visit adherence, a system must be in place to capture that information. It is important that in order to make a complete recommendation on the measure of retention that most appropriately defines a poor or optimal retainer, all measures of retention must be evaluated and compared in future studies.

Future Research

Retention in medical care among individuals living with HIV should be given major attention as those who are optimally retained in care have been consistently shown to achieve more favorable outcomes, like viral suppression, compared to those who are not optimally retained in care. Although researchers have consistently shown the negative impact poor retention has on health outcomes, more research still needs to be conducted in this area. First, it is important for clinicians and researchers to adopt one measurement of retention and use it consistently throughout studies, which can make comparison of studies

easier. A guideline should be set which states what constitutes poor or optimal retention and what measure should be used to determine retention (i.e. missed visits, visit constancy, HRSA, etc.).

Chapter Three provided a recommendation to help clinicians and researchers determine which measure may appropriately define retention, but not all measurements could be evaluated in the study due to the resources available, so future studies should be conducted where all measures of retention can be compared to have a recommended retention measure set in place.

It is important for researchers to understand the factors that may impact retention that go beyond the normal socio-demographic and clinical characteristics, as this may help HIV clinicians and researchers develop interventions that can help reduce the barriers to optimal retention. For example, referring patients to service organizations that may assist with transportation or housing can be beneficial in increasing retention among this population. Providing treatment referrals or behavioral interventions to patients with substance abuse disorders may be beneficial to the patient who is seeking HIV medical care. There is limited published data that suggests which interventions are most effective at maintaining optimal retention, and which interventions work for specific groups. Some researchers have suggested that care coordination, which links patients to an individual (e.g. case manager or social worker) once they have initiated care, may help the patient better navigate the healthcare system which in turn helps them maintain consistent contact with their medical provider.[53-55] Researchers need to publish and share their work, so other researchers interested in providing interventions can replicate their study. Also studies need to be conducted that randomizes patients into different intervention strategies to see which strategy may work best in keeping patients retained in care.

A longitudinal assessment of retention is urgently needed as most studies have typically restricted their time to one to three years. It is important to understand how retention changes over time and incorporating a longitudinal study of retention will provide insight on who the individuals are that are falling out of care and insight into how these individuals may be re-engaged back into care. Resources and funding should be made available so longitudinal studies can be conducted and resources are needed to develop strategies to bring those who have fallen out of care back into care.[14]

This dissertation focused on one single facility (BCC), which meant that the results could not be generalized to any other HIV population seeking medical care. Studies focusing on retention should consider multi-site studies especially within each state and nationally to determine overall retention. Clinicians and researchers, from multiple clinic sites, should be open to collaborating together. A future study in Kentucky will be to collaborate with the other RW funded clinics and determine retention and the barriers that impact optimal retention. It is also important to conduct multi-site studies within the state as patients may be in continuous care, but accessing care at different clinics. A patient seeking HIV medical care may change providers for numerous reasons, and having all clinics on board can ensure that the patient is actually considered an optimal retainer.

Retention in care should remain a major priority for clinicians and researchers as this can improve the health of individuals living with HIV as well as potentially reduce the incidence of new infections.

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HIV/AIDS Branch Epidemiologist and Research Analyst

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Graduate Research Assistant 01/11 – 01/12

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Graduate Research Assistant 05/09 – 01/12

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Summer Research Assistant 06/10 – 08/10

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ACADEMIC EXPERIENCE

University of Kentucky, Lexington, KY
College of Medicine, Department of Internal Medicine
Guest Lecturer 2012

- Introduction to Biostatistics

University of Kentucky, Lexington, KY
Department of Epidemiology
Guest Lecturer 2011

- CPH 605: Introduction to Epidemiology

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- Global Health

Department of Biostatistics
Tutor 2010-2011

- STA 580: Biostatistics I
- CPH 630: Biostatistics II

Department of Biostatistics
Teaching Assistant 2009-2010

- CPH 535: SAS Database Programming

Department of Biostatistics
Teaching Assistant 2008-2009

- CPH 630: Biostatistics II

PUBLICATIONS

1. Coker AL, Follingstad D, Garcia LS, Williams CM, **Crawford TN,** Bush HM. (2012). Association of Intimate Partner Violence and Childhood Sexual Abuse with Cancer-Related Well-Being in Women. *Journal of Women's Health.* (In Press).

2. Coker AL, Garcia LS, Williams CM, **Crawford TN,** Clear ER, McFarlane J, Ferguson JE. (2012). Universal psychosocial screening and adverse pregnancy outcomes in an academic obstetric clinic. *Obstetrics and Gynecology.* 119(6): 1180-9.

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4. **Crawford T,** Caldwell G, Bush HM, Browning S, Thornton A. (2012). Foreign Born Status and HIV/AIDS: A Comparative Analysis of HIV/AIDS Characteristics Among Foreign and U.S. Born Individuals. *Journal of Immigrant and Minority Health*. 14 (1): 82-88.

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6. Mendiondo M, Alexander L, **Crawford T.** (2010). Health Profile Differences for Menthol and Non-Menthol smokers: Findings from the Nation Health Interview survey. *Addiction.* 105 (Suppl. 1), 124-140.

7. Alexander L, **Crawford T,** Mendiondo M. (2010). Occupational Status, Work-site Cessation Programs and Policies, and Menthol Smoking on Quitting Behaviors of US Smokers. *Addiction.* 105 (Suppl. 1), 95-104.

MANUSCRIPTS IN SUBMISSION

1. Hambleton MT, Reynolds EW, Sithisarn T, Traxel SJ, Patwardhan AR, **Crawford TN,** Mendiondo MS, Bada HS. Autonomic System Function (Heart Rate Variability) after Prenatal Opiate Exposure. (Submitted to Archives of Diseases in Childhood).

2. **Crawford TN,** Sanderson W, Thornton A. A Comparison Study of Methods for Measuring Retention in HIV Medical Care. (Submitted to the Journal of AIDS and Behavior).

ABSTRACTS

1. **Crawford T,** Sanderson WT, Thornton A. A Comparison Study of Multiple Methods in Measuring Retention to HIV Medical Care: Determining the Impact Retention has on Viral Load Suppression. College of Public Health Research Day Symposium. Lexington, KY. (2012). – 3rd place award

2. **Crawford T,** Caldwell Glyn, Bush HM, Browning S, Thornton A. Foreign-born Status and HIV… A Comparison Analysis of HIV and its Progression to AIDS among Foreign and U.S. Born Individuals in Lexington, KY. College of Public Health Research Day Symposium. Lexington, KY. (2010). – 1st place award

3. Hong-McAtee I, Whitehead V, **Crawford T,** Grider D, Stevens S, Bada H, Kriss VM, Desai N. Thyroid Volume Increases with Gestational Age. Pediatric Academic Societies Meeting. Vancouver, BC Canada. (2010).

4. Reid T, Bendure L, Bada H, **Crawford T,** Reynolds E, Granger D, Mendiondo M. Characteristics of Rural Women who used Illicit Drugs During Pregnancy. Center for Clinical and Translational Science Spring Conference. Lexington, KY. March 23, 2010.

5. Bendure L, Reid T, Bada H, **Crawford T,** Reynolds E, Granger D, Mendiondo M. Effects of Prenatal Illicit Drug Exposure on the Neonate and Opiate Exposure on Fetal Growth. Center for Clinical and Translational Science Spring Conference. Lexington, KY. March 23, 2010.

PROFESSIONAL AND UNIVERSITY SERVICE

- Referee, Journal of Immigrant and Minority Health
- Referee, Journal of Addiction
- College of Public Health Task Force Committee Member, 2012
- Member, Council of State and Territorial Epidemiologists, 2012-Present
- President, UK School of Public Health Association, Lexington KY, 2008-2009
- UK College of Public Health, Student Administrative Council, 2008-2009
- Member, American Statistical Association, 2010-Present
- Member, American Public Health Association, 2008-2010
- Member, Kentucky Public Health Association, 2007-2010
- VP of Service, Alpha Phi Omega, 2006-2007

HONORS AND AWARDS

- College of Public Health's Research Day Symposium – 3rd place Poster Presentation, 2012
- College of Public Health's Research Day Symposium - Outstanding Poster Presentation, 2010
- Service Award (College of Public Health Graduation Awards), University of Kentucky, 2009
- Lyman T Johnson Scholarship Recipient, 2007-2009
- National Math and Science Grant Recipient, 2007
- National Society of Collegiate Scholars, 2004-2007
- African American Achiever Scholar, 2003-2007